Review Articles

1. Who are at high risk of mortality and morbidity among children with congenital heart disease undergoing noncardiac surgery?
2. Perioperative glucocorticoid management based on current evidence
3. Safety of epidural steroids: a review
Aims and Scope

Anesthesia and Pain Medicine (APM) is the official scientific journal of Korean Society of Neuroscience in Anesthesiology and Critical Care (KSNACC), The Korean Society for Anesthetic Pharmacology (KSAP), The Korean Society of Obstetric Anesthesiologists (KSOA), The Korean Society of Pediatric Anesthesiologists (KSPA), Korean Neuromuscular Research Society (KNRS), Korean Society of Cardiothoracic and Vascular Anesthesiologists (KSCVA), Korean Society of Transplantation Anesthesiologists (KSTA), The Korean Spinal Pain Society (KSPS), Korean Society of Regional Anesthesia (KSRa), and Korean Society for Airway Management (KSAM). The abbreviated title is “Anesth Pain Med”. It is published four times a year on the last day of January, April, July, and October in English. The mission of APM is to improve safety and quality of care of related patients and clinical practice of anesthesiologists by publishing definitive articles in the field of anesthesiology including practice of perioperative management, critical care, and pain medicine. The scopes of APM are as follows: anesthesia-related issues from affiliated neuroanesthesiology (KSNACC), experimental, laboratory works or clinical relevance of anesthetic pharmacology (KSAP), anesthesia for operative delivery, pain relief in labor, care of the critically ill parturient, perinatal physiology and pharmacology (KSOA), anesthetic care, perioperative management, and alleviation of pain in children (KSPA), physiology of neuromuscular transmission and block, pharmacology of neuromuscular blocking agents and their reversal agents, principles and applications of neuromuscular monitoring, and drug interaction between neuromuscular blocking agents and other substances (KNRS), anesthesia for cardiothoracic and vascular surgery and management of patients undergoing various surgeries for patients with cardiac, pulmonary, and vascular diseases (KSCVA), perioperative anesthesia care of transplantation surgery, physiology or pharmacology related with transplantation anesthesiology (KSTA), pathophysiology, pharmacology, and all aspects of spine related pain (KSPS), clinical techniques of regional blocks, anatomy, patient safety issues, basic sciences such as pharmacology of local anesthetics or sedative drugs (KSRa), all fields of airway management including difficult airway and complications (KSAM).

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EXPERIENCE THE BRIDION EFFECT

Bridion (sugammadex) offers significantly fast and predictable recovery in most patients with profound rocuronium-induced neuromuscular blockade (NMB). 1, 2

Reappearance of T 1: For reversal of a NMB: 98% of Bridion (sugammadex) patients had recovered to a TOF ratio of 0.9 compared with only 11% of neostigmine patients within 5 minutes. In comparison, it took 101 min for 98% of patients receiving neostigmine to recover to a TOF ratio of 0.9. 3

Reappearance of 1–2 PTCs: 98% of Bridion (sugammadex) patients had recovered to a TOF ratio of 0.9 compared with only 11% of neostigmine patients within 5 minutes.

The median (interquartile range) time to recovery of the TOF ratio to 0.9 was 2.7 (1.2–161) vs 2.1–43) min in the Bridion (sugammadex) group versus 490 min in the neostigmine group. 4

Indication of Bridion is reversal of neuromuscular blockade induced by rocuronium or vecuronium. 5

The safety and efficacy of Bridion for pediatric and adolescent patients under the age of 18 has not been established. 6

* For more information, please refer to the full prescribing information.

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**BRIDION Safety Information**

Withdrawal of neuromuscular blockade (WNB) (Dosage and Administration). Dose reduction: A dose of 4 mg/kg Bridion is recommended as a single bolus injection if recovery has reached at least 1 h post-injection (caution should be used for bridging of rocuronium and vecuronium-induced blockades). A dose of 2 mg/kg Bridion is recommended as a single bolus injection if recovery has occurred at the end of a session with bridging of rocuronium and vecuronium-induced blockades. Dose adjustments are not necessary. Obesity Patients: The dose of Bridion should be adjusted according to body weight. Patients with hepatic impairment: Patients with mild or moderate hepatic impairment need no dose adjustment. Dose for renal impairment: Mild or moderate renal impairment: Patients with mild or moderate renal impairment need no dose adjustment. Patients with severe renal impairment: Dose adjustment should be considered. See the Warnings section for more information. 7

**Precautions**

Cardiovascular: Most patients will have mild postoperative hypotension. See the Precautions section for more information. 8

**Contraindications**

Hypersensitivity to any component of this product. 9

**Cautions**

see the Warnings and Precautions section for more information. 7

**Adverse Reactions**

The incidence of adverse events observed in the postmarketing period of Bridion is comparable to those observed in clinical studies. The incidence of adverse events reported in the postmarketing period is: 0.1% – 1%: anaphylaxis; 1% – 10%: allergic reactions; 10% – 20%: urticaria; 20% – 40%: rash; 40% – 60%: hypotension; 60% – 80%: anaphylactic events; 80% – 100%: allergic reactions; 100%: injection site reactions. 10

**Dosage and Administration**

Bridion (sugammadex) is a single-dose vial containing 15 mg of Bridion (sugammadex). It is usually administered as a single intravenous dose. The recommended dose is 1 mg/kg. The maximum dose per patient is 200 mg. 11

**How Supplied**

Bridion is available as a lyophilized powder in 15 mg vials. 12

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* Before administering BRIDION, please read the full prescribing information.

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References:

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Does PONV still Remain unsolved?

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INTRODUCTION

The incidence of congenital heart disease (CHD) is reported to be about 6 per 1,000 full-term live births in the United States [1]. With advances in the perinatal diagnosis of CHD and improvement in surgical and medical management, the survival rate and life expectancy in children with CHD have been increasing [2]. These children frequently require noncardiac surgeries, including laparoscopic, urogenital, and otolaryngological surgeries. During the first year of life, 41% of infants who underwent congenital heart surgery had undergone noncardiac surgery by the age of 5 years [3]. With an increasing demand for surgical procedures under general anesthesia in these patients, it is not uncommon for anesthesiologists to encounter children with an unrepaired CHD or residual pathologic conditions, as well as children with a repaired CHD. Therefore, it is important to identify children at risk of perioperative morbidity and mortality and to understand their pathophysiologic and hemodynamic status when preparing their general anesthetic plan. In the following review, we discuss the current knowledge regarding children with CHD who have high anesthesia and surgical risks and also focus on the perioperative considerations for these high-risk patients.

RISKS OF NONCARDIAC SURGERIES IN CHILDREN WITH CHD

Recently, mortality and perioperative adverse events related to noncardiac surgeries have been reported in children studies with large sample populations, including those with and without CHD. Baum et al. [4] showed that the overall 30-day mortality after noncardiac procedures was higher in patients with CHD (6.0%) than in those without CHD (3.8%). They also found that age, complexity of
the operation, and CHD, were associated with perioperative mortality. In the Pediatric Perioperative Cardiac Arrest (POCA) Registry, causes of anesthesia-related cardiac arrest were reported from nearly 80 voluntarily enrolled North American institutions that provide anesthesia for children over a period of 10 years [5]. In this study, children with CHD had a higher mortality rate (33%) than those without CHD (26%). Cardiac arrest was strongly associated with surgical complexity and the patient’s underlying functional status. Among the types of CHD, single ventricular physiology, aortic stenosis, and cardiomyopathy were associated with the highest mortality following a cardiac arrest. In another study, the incidence of perioperative cardiac arrest was 2.9 per 10,000 anesthetic episodes among patients undergoing noncardiac surgeries, and of these, 27% had CHD [6]. In addition, they found that the most common causes of cardiac arrest during noncardiac surgeries were hypovolemia, bleeding, and massive transfusion. These findings suggest that intrinsic surgical factors and the associated hemodynamic deterioration are important for estimating the risk of cardiac arrest. In a study investigating 101,885 anesthetic cases, the overall 24-h mortality after anesthesia was 13.4 per 10,000 [7]. The highest incidence of death was in children younger than 30 days. Collectively, children with CHD are faced with a high risk of mortality and adverse events related to anesthesia when undergoing noncardiac surgeries. In particular, the complexity of CHD is regarded as an important factor influencing high risk of mortality. Therefore, children with CHD may be at higher risk of mortality and morbidity during and after noncardiac surgeries. In addition, age, anatomical and functional status according to CHD complexity, and intrinsic surgical risks are points that must be considered with care when estimating the risks of mortality and morbidity.

The other issue to consider is how to define and stratify the risk factors. According to the American College of Surgeons who collected data on noncardiac surgeries as a part of its National Surgical Quality Improvement Program for the classification of CHD, CHD can be stratified as minor, major, and severe, based on the residual lesion burden and the functional status of the heart [8]. According to this classification, children who have maintained good cardiac conditions with or without medication and children with a repaired CHD are classified as having minor CHD; patients with a repaired CHD but who have residual abnormalities in hemodynamic status are considered to have major CHD; patients with an unrepaired cyanotic CHD, pulmonary hypertension, or ventricular dysfunction or children awaiting transplantation are classified to have severe CHD. After propensity matching for age, sex, physical status, surgical emergency, and surgical complexity, severe CHD was significantly associated with 30-day mortality and overall mortality [8]. However, there was no difference between children with minor CHD and their matched controls. In addition to perioperative mortality, morbidities including postoperative reintubation, infections, renal failure, neurologic complications, thrombotic events, reoperation, and readmission were more frequent in patients with major and severe CHD. In a recent study regarding surgical complexity, children with CHD younger than 1 year showed a greater risk of postoperative complications, with an incremental increase in odds ratios in the order of minor, major, and severe CHD [9]. In another study of 3,010 children with CHD undergoing noncardiac surgeries, major and severe CHD remained significant risk factors for perioperative cardiovascular events after adjusting for the American Society of Anesthesiologists physical status, emergency cases, and surgical types [10].

In a previous study using a risk stratification tool to classify risk levels for perioperative cardiac complications, repaired atrial defects and ventricular septal defects were considered low risk, maintenance cardiac medications; and repaired cyanotic or complex CHD were classified as moderate risk; and unrepaired cardiac anomalies, Williams syndrome, pulmonary hypertension, valvular heart disease with significant valvular gradients, hypertrophic cardiomyopathy with obstruction, congestive heart failure, or children with ventricular-assisted devices were considered high risk [11]. To further determine the anesthesia risk, age less than 1 year, comorbidities, and surgical complexity were included as the next step. Similarly, results from non-validated data of anesthesia for noncardiac surgeries indicated that children with CHD were classified as low, intermediate, and high risk, and further discriminated based on physiological decompenation, complexity of the CHD, major surgery, age under 2 years, emergency, preoperative hospital stay more than 10 days, and American Society of Anesthesiologists physical status [12,13].

To date, only one study has reported a risk assessment model using a validation cohort. This study identified eight preoperative factors that were significant in determining in-hospital mortality: 1) emergency procedure, 2) severe CHD, 3) previous surgery within the last 30 days, 4) single
ventricular physiology, 5) inotropic use, 6) cardiopulmonary resuscitation, 7) kidney injury, and 8) mechanical ventilation [14]. Based on the variables obtained from multivariable logistic regression analyses, scores from 0 to 10 were determined. This scoring system showed good discrimination and calibration with an area under the receiver operating characteristic curve of 0.831 (95% confidence interval: 0.787–0.875) in the validation cohort. Briefly, scores ≤ 3 were associated with low risk, scores of 4–6 were associated with medium risk, and scores ≥ 7 were associated with a high risk for mortality (odds ratios 1.54, 4.19, and 22.15, respectively) [14]. Notably, major and severe CHD, including single ventricular physiology, were found to be major determinants of perioperative outcomes [14]. In contrast, surgical complexity was not significant [14]. They also highlighted that scoring-based risk stratification for mortality may be necessary to help guide the perioperative management of patients with high-risk CHD.

Herein, we reviewed the perioperative considerations of children undergoing noncardiac surgeries who were classified as having high-risk CHD, in common with most of the previously reported studies.

**SINGLE VENTRICULAR PHYSIOLOGY**

It is critical that anesthesiologists understand the physiology of each palliative stage of a single ventricle, which includes truncus arteriosus, large and multiple ventricular septal defects, and hypoplastic left heart syndrome (HLHs). Patients who have not undergone completion of superior cavopulmonary anastomosis (SCPA) are known to have the highest risks during noncardiac surgeries and congenital heart surgery. Especially in HLHs, the mortality rate of patients younger than 2 years has been reported to be up to 19% after noncardiac surgeries [15]. Hemodynamic derangement is caused by excessive pulmonary blood perfusion and poor systemic perfusion from imbalanced circulation, decreased coronary perfusion, impairment of the systemic right ventricle, and atrioventricular valve dysfunction. As the single ventricle concurrently operates both the pulmonary and systemic circulations, hemodynamic balance is frequently disrupted by alterations in pulmonary and systemic vascular resistance (PVR and SVR, respectively), ventilatory strategy including hypoxia and hypercapnia, acid-base balance, and intravascular volume status. Therefore, postponing elective noncardiac procedures under after SCPA is recommended. If the patient could not postpone due to an emergent condition, Pulmonary-to-systemic blood flow ratio should be at or just below 1 to maintain systemic perfusion and optimize oxygen delivery, consequently resulting in arterial oxygen saturation of 80–90% [16].

After the SCPA, the single ventricle is no longer operating with the volume overloading required to sustain parallel circulations. Accordingly, cardiac output and systemic perfusion are not entirely dependent on pulmonary blood flow, which makes the hemodynamic performance relatively stable. However, hypercarbia, acidosis, and elevated airway pressure should be avoided because pulmonary blood flow remains dependent on PVR. However, hypocarbia may exacerbate a decrease in cerebral blood flow and reduce venous return from the brain and upper body [17].

If there is high pressure in the superior vena cava, the head and the tongue may become congestive due to disturbance in venous return. In these patients, the goal of anesthetic management is to maintain systemic oxygenation with adequate pulmonary blood flow, which is secured by optimizing intravascular volume, minimizing airway pressure, and ensuring a low PVR.

Finally, the destination of single ventricular physiology is the completion of successful Fontan circulation, in which all systemic venous return is composed of pulmonary blood flow. Even though systemic arterial saturation is maintained above 90%, cardiac output relies on pulmonary blood flow that runs down passively because there is no pump function producing a pulsatile driving pressure. Pulmonary blood flow and cardiac output are strictly influenced by mechanical ventilation with positive end-expiratory pressure [18,19]. In addition, the pressure of the systemic venous system is elevated, and its capacitance is decreased, and accompanied by diminished recruitment reserve of the vascular volume [20]. Consequently, patients with a Fontan circulation are intolerant of vasodilation from anesthetic agents, surgical bleeding, and dehydration. It may be beneficial to prepare inotropic agents and vasopressors for the treatment of hypotension and avoid excessive volume challenges [20]. Unfortunately, bleeding tendency may be increased due to persistent high venous pressure and anticoagulant therapy. However, they also have thrombosis risks [21]. Along with preloading, other factors are required to achieve the perfect Fontan circulation as follows: low PVR, sinus rhythm, normal atrioventricular valve function, good ventricular performance, and the absence of inflow and outflow tract obstruction [22] (Fig. 1). After surgery, it
can be favorable for patients with Fontan physiology to extubate as early as possible and restore spontaneous breathing.

**SUPRASYSTEMIC PULMONARY HYPERTENSION**

Pulmonary hypertension is one of the factors associated with a high perioperative mortality rate. The perioperative mortality risk has been reported to be at least 20-fold greater in children with pulmonary hypertension than in those without among children undergoing noncardiac procedures [23]. Suprasystemic pulmonary hypertension is defined as the ratio of mean or systolic pulmonary artery pressure to systemic artery pressure (PAP/SAP) of > 100%. As pulmonary hypertension progresses, perioperative outcomes worsen. Thus, it is crucial to determine the severity of pulmonary hypertension during preoperative evaluation. Features that distinguish the severity of pulmonary hypertension are as follows: right ventricular (RV) dysfunction on echocardiography, decreased functional capacity, growth failure, significantly elevated brain natriuretic peptide (BNP) or N-terminal pro-BNP levels, and poor catheterization indices [24]. In these children who are chronically exposed to suprasystemic PAP, acute RV failure and pulmonary hypertensive crisis may occur given the limited functional reserve of the RV. If coronary hyperperfusion occurs simultaneously, catastrophic results such as myocardial ischemia, fatal arrhythmia, and cardiac arrest may occur even if the increase in PAP is small [25].

Whenever patients undergo surgery and general anesthesia, pulmonary hypertensive crisis can develop due to various causes including hypoxia, hypercarbia, acidosis, hypothermia, and sympathetic stimulation. Particularly in children whose PVR increases but remains responsive and modifiable, any causes that induce an increase in PAP can trigger a vicious cycle of pulmonary hypertensive crisis [25] (Fig. 2). During anesthesia, clinical signs manifest as arterial desaturation and low end-tidal CO₂ levels due to impaired pulmonary blood flow, sudden cardiovascular collapse, hypotension, and tachy- or brady-arrhythmia. Pulmonary hypertensive crisis should be treated promptly. Management of pulmonary hypertensive crisis may involve ventilation with 100% inspired O₂, mild hyperventilation, inhaled nitric oxide, alkalinization using sodium bicarbonate infusion, and inotropic support.

**LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION**

According to the POCA registry, 16% of anesthesia-related cardiac arrest was caused by obstruction to ventricular outflow such as supravalvular, subaortic, or aortic stenosis [5]. After cardiac arrest in these patients, the mortality rate was 62%, suggesting that anesthesiologists should be meticulous in perioperative management. In patients with Williams syndrome, cardiovascular abnormalities are characterized by supravalvular aortic and pulmonary stenoses.
with elastin arteriopathy. Ventricular outflow obstruction is followed by myocardial hypertrophy. Worsening biventricular hypertrophy may lead to sudden cardiovascular collapse in patients undergoing anesthesia. Moreover, factors related to coronary blood flow may also contribute to cardiovascular events during the perioperative period including 1) Anatomical abnormalities and coronary artery stenosis, 2) compromise of diastolic blood pressure caused by loss of aortic distensibility, and 3) myocardial oxygen imbalance from increased demand of hypertrophied myocardium [26]. Prolongation of the corrected QT interval is present in 13% of patients with Williams syndrome, and this is associated with sudden cardiac arrests [27]. According to examinations conducted as a part of preoperative evaluation, children with Williams syndrome can be classified to have a low, moderate, or high risk. However, regardless of the risk classification, anesthetic management is performed while attempting to maintain sinus rhythm, and ensuring the maintenance of contractility, restoration of intravascular volume deficit, and preservation of SVR [27]. Therefore, the choice of anesthetic agents must be guided by whether a drug induces abrupt hemodynamic perturbation.

**CARDIOMYOPATHY**

Children with cardiomyopathy and ventricular dysfunction are classified to have high perioperative mortality and morbidity risks related to anesthesia [8]. Based on the POCA registry, cardiomyopathy contributed to 13% of perioperative cardiac arrests [5]. The etiology of cardiomyopathy includes idiopathic causes (hypertrophic, restrictive, and dilated), structural heart disease (such as CHD including single ventricular physiology), and secondary disorders (such as end-stage renal disease and congenital heart block) [28]. Among these children, there may be an increased risk of preoperative morbidity and mortality when ventricular dysfunction is caused by dilated cardiomyopathy, failing Fontan circulation, left ventricular outflow obstruction, and pulmonary hypertension. General anesthesia may induce hemodynamic instability even at regular doses of anesthetic agents because ventricular functional reserve is severely compromised. Ketamine is recommended as the choice of induction agent because the sympathetic tone is preserved. In addition, balanced anesthesia is beneficial for achieving hemodynamic stability using opioids, volatile agents, neuromuscular blockade, or a combination of these agents [29]. In children with cardiomyopathy, the anesthetic goal is to maintain the preload, sinus rhythm, SVR, ventricular contractility, and coronary perfusion. Inotropic and vasoactive drugs may be frequently required to manage hypotension and low cardiac output. It is important that an excessively elevated SVR be avoided because an impaired ventricle with limited
contractile reserve is not tolerant of a high afterload [30].

**CONCLUSION**

Children with CHD, particularly single ventricular physiology, suprasystemic pulmonary hypertension, left ventricular outflow obstruction, and cardiomyopathy with ventricular dysfunction, have the highest morbidity and mortality risks following noncardiac surgeries. During the preoperative evaluation of these patients, it is necessary to identify whether residual functional or anatomical impairment is present at the time of surgery. To prevent poor outcomes and avoid worse-case scenarios, anesthesiologists should be fully acquainted with the pathophysiology of CHD and be able to respond to intraoperative events and complications during surgery in a timely manner.

**CONFLICTS OF INTEREST**

No potential conflict of interest relevant to this article was reported.

**AUTHOR CONTRIBUTIONS**

Conceptualization: Won-Jung Shin, In-Kyung Song. Writing - original draft: In-Kyung Song. Writing - review & editing: Won-Jung Shin.

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INTRODUCTION

Synthetic glucocorticoids were first introduced in 1949 after the development of a purified preparation, known as cortisone, and became a revolutionary treatment for patients with primary adrenal failure and other acute-chronic inflammatory and autoimmune diseases. In anesthesiology, it is widely used to treat reactive airway diseases, acute nerve injury, nausea or vomiting, inflammatory diseases, and excessive immunosuppression during organ transplantation or cardiopulmonary bypass [1]. Shortly after the development of synthetic cortisone, there were two case reports of perioperative secondary adrenal crisis. The two young patients on long-term cortisone therapy stopped their steroids before the surgery; they suddenly died after the surgery, and the result of the autopsy showed bilateral adrenal atrophy [2,3]. Since then, it has become common practice to perioperatively administer glucocorticoids at a supra-physiological dose, the so-called stress-dose, to patients on steroid therapy for long duration and in suspected cases of adrenal insufficiency.

Glucocorticoid preparations, adreno-cortical steroids, with strong anti-inflammatory and immunosuppressive effects, are widely used for treating various diseases. The number of patients exposed to steroid therapy prior to surgery is increasing. When these patients present for surgery, the anesthesiologist must decide whether to administer perioperative steroid supplementation. Stress-dose glucocorticoid administration is required during the perioperative period because of the possibility of failure of cortisol secretion to cope with the increased cortisol requirement due to surgical stress, adrenal insufficiency, hemodynamic instability, and the possibility of adrenal crisis. Therefore, glucocorticoids should be supplemented at the same level as that of normal physiological response to surgical stress by evaluating the invasiveness of surgery and inhibition of the hypothalamus-pituitary-adrenal axis. Various textbooks and research articles recommend the stress-dose of glucocorticoids during perioperative periods. It has been commonly suggested that glucocorticoids should be administered in an amount equivalent to about 100 mg of cortisol for major surgery because it induces approximately 5 times the normal secretion. However, more studies, with appropriate power, regarding the administration of stress-dose glucocorticoids are still required, and evaluation of patients with possible adrenal insufficiency and appropriate glucocorticoid administration based on surgical stress will help improve the prognosis.

Keywords: Adrenal glands; Adrenal insufficiency; Glucocorticoids; Hypothalmus; Perioperative period; Pituitary gland; Steroids.
Physiology of adrenocortical hormone secretion: hypothalamic-pituitary-adrenal axis

Adrenocorticosteroids are steroid derivatives produced in the adrenal cortex and include three endogenous hormones: glucocorticoid, mineralocorticoid, and androgen. All of them are synthesized when cholesterol is converted to pregnenolone by the cytochrome P450 enzyme [1]. Of these, glucocorticoids are secreted from the zona fasciculata of the adrenal cortex and the most important glucocorticoid is cortisol. Cortisol is an essential hormone for maintaining life. It mediates carbohydrate and protein metabolism, fatty acid transfer, electrolyte and fluid balance, and anti-inflammatory reactions. Cortisol enables the synthesis and release of catecholamines and contributes to normal vascular permeability, vascular tone, and myocardial contraction by regulating β-receptor synthesis and regulation [1].

The secretion of adrenal cortical hormones is regulated by the hypothalamic-pituitary-adrenal (HPA) axis. The corticotropin-releasing hormone (CRH) secreted from the hypothalamus stimulates the secretion of adrenocorticotropic hormone (ACTH) in the anterior pituitary gland, and ACTH stimulates the adrenal gland. This positive feedback for cortisol secretion and negative feedback for inhibiting the secretion of CRH and ACTH due to increased cortisol concentration regulates the secretion of cortisol [1].

The secretion of cortisol changes depending on the pulsatile secretion of CRH and ACTH according to the circadian rhythm. Serum cortisol concentration reaches the highest concentration of about 15 μg/dl around 6–9 am, then drops to the lowest concentration of below 2 μg/dl around 11 pm to 1 am. The median value of the 24-h period is approximately 5.2 μg/dl [9]. In normal adults, the adrenal glands produce approximately 5 to 10 mg/m²/day (body surface area per day) of cortisol, which is equivalent to 5 to 7 mg of oral prednisone or 20 to 30 mg of hydrocortisone [10,11]. In plasma, approximately 90% of circulating cortisol binds to corticosteroid-binding globulin (CBG), an α₂-globulin binding protein synthesized in the liver [12]. The remaining 5–10% binds to albumin or circulates freely and exerts an effect on target cells. When plasma cortisol concentration exceeds 20–30 μg/dl, CBG is saturated, and the concentration of free cortisol increases rapidly [12].

Sudden physiological and mental stress such as trauma, burns, major surgery, hypoglycemia, high fever, low blood pressure, severe exercise, and cold exposure activates the HPA axis and increases blood ACTH and cortisol levels. In a normal response to stress, the blood cortisol concentration increases to 18–20 μg/dl and adrenal cortisol secretion increases up to 30–45 μg/dl during moderately stressful situations and about 260 μg/dl in a highly stressful life-threatening situation. Increased cortisol levels normalize within approximately 24 to 48 h after the stress is resolved [11].

Adrenal insufficiency

Adrenal insufficiency (AI) is the inability of the adrenal glands to produce adequate amounts of corticosteroids in response to various pathophysiologic states; this condition can be classified into primary, secondary, and tertiary AI depending on the cause [11]. Primary AI is an abnormality in the adrenal gland itself and is caused by the destruction of the adrenal cortex due to autoimmune diseases, viral and tuberculosis infection, hemorrhage, metastatic cancer, and sepsis. Secondary AI is rare but is caused by impaired production of ACTH or CRH due to damage or dysfunction caused by diseases of the pituitary gland or hypothalamus. Tertiary AI is the most common form, widely included in secondary AI, and is typically caused by inhibition of the hypothalamus or pituitary due to iatrogenic corticosteroid therapy; the degree of adrenal dysfunction is variable and sometimes reversible. In these patients, mineralocorticoid secretion is not affected and only cortisol production is reversibly inhibited [13]. Tertiary AI rarely occurs when oral prednisone dosage is less than 5 mg or when steroid is tak-
rarily, and the serum concentration of cortisol rises due to surgery, the diurnal secretion of cortisol malfunctions temporarily, that is, 75–150 mg/day in cortisol secretion up to approximately 5–10 times the cortisol levels increase proportionally, resulting in an increase in cortisol secretion due to surgery, proinflammatory cytokines, CRH, ACTH, and corticotropin-releasing hormone (CRH). During major surgery, immune, and cardiovascular effects. During major surgery, pressors should be immediately recognized and corrected by the administration of stress-doses of steroids, fluids, and vasopressors.

**Clinical signs of adrenal crisis**

Patients with long-term steroid administration or severe illness have a reduced cortisol response to stress, which causes risk of an acute adrenal crisis. Symptoms of acute adrenal crisis in awake patients are presented in **Table 1** [15]. In patients under anesthesia, hypotension, which does not respond to fluid administration, has been considered the most important sign of perioperative adrenal crisis [7]. Symptoms and signs that occur earlier than hypotension include non-specific changes in consciousness and cognitive decline and persistent fever [8]. Laboratory examinations may show hypoglycemia, hyponatremia, and hyperkalemia. Since most of these symptoms are non-specific, it is necessary to exclude causes other than AI. However, since adrenal crisis is a life-threatening condition, it should be immediately recognized and corrected by the administration of stress-doses of steroids, fluids, and vasopressors [8].

**Surgery Induced Cortisol Stress Response**

Surgery causes a stress response with a wide range of endocrine, immune, and cardiovascular effects. During major surgery, proinflammatory cytokines, CRH, ACTH, and cortisol levels increase proportionally, resulting in an increase in cortisol secretion up to approximately 5–10 times the normal secretion, that is, 75–150 mg/day [16,17]. After surgery, the diurnal secretion of cortisol malfunctions temporarily, and the serum concentration of cortisol rises due to surgical stress [11].

In a recent meta-analysis, the change in serum cortisol concentration before and after surgery in patients without steroid therapy was analyzed in 71 studies since the 1990s [18]. In this study, the invasiveness of surgery was divided into three stages from grade 1 to 3 according to the modified Johns Hopkins surgical criteria [19]. Minor to moderately invasive procedures with less bleeding (potential blood loss < 500 ml) were included in grade 1; for example, breast biopsy, removal of minor skin or subcutaneous lesions, myringotomy tubes, hysteroscopy, cystoscopy, vasectomy, circumcision, fiberoptic bronchoscopy, diagnostic laparoscopy, dilatation, and curettage. Moderately to significantly invasive procedures (potential blood loss 500–1,500 ml) were included in grade 2; for example, thyroidectomy, hysterectomy, myomectomy, cystectomy, cholecystectomy, laminectomy, hip/knee replacement, nephrectomy, and major laparoscopic procedures. Highly invasive procedures (potential blood loss > 1,500 ml) were included in Grade 3, for example, major reconstruction of the gastrointestinal tract, major genitourinary surgery, cardiothoracic procedures, and intracranial procedures. In this review, it was found that the grade of surgery significantly affected cortisol secretion [18]. Patients undergoing grade 1 surgery did not show an intraoperative cortisol peak, and postsurgical cortisol concentrations were similar to those at baseline. Nevertheless, when compared to published data on healthy, unstressed adults, the mean cortisol output over the first 24 h after grade 1 surgical procedure was approximately doubled. Patients undergoing grade 2 and 3 surgery had 3.5–4 times higher cortisol output than that of healthy, unstressed individuals within the first 24-h postoperative period. Moreover, in both grade 2 and 3 surgeries, mean cortisol values remained elevated in comparison with the baseline measurements up to postoperative day 7.

Due to ethical issues, only a few studies have investigated the change in cortisol concentration and the incidence of AI after discontinuation of steroids in patients taking steroids. In 1973, Kehlet and Binder [16] investigated the occurrence of acute AI after steroid discontinuation in 73 patients undergoing major surgery, including splenectomy and colon resection. Patients took 5–80 mg of prednisone for various periods in this study. As a result, about 10% of patients developed perioperative hypotension, but only 3 patients showed low blood cortisol levels, and most of them were treated by fluid administration. They also measured cortisol concentration in patients undergoing major

<table>
<thead>
<tr>
<th><strong>Table 1. Signs of Adrenal Crisis [15]</strong></th>
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<tbody>
<tr>
<td>Signs of adrenal crisis</td>
</tr>
<tr>
<td>Dehydration, hypotension</td>
</tr>
<tr>
<td>Nausea and vomiting with a history of weight loss and anorexia</td>
</tr>
<tr>
<td>Abdominal pain (“acute abdomen”)</td>
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<tr>
<td>Unexplained hypoglycemia</td>
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<tr>
<td>Unexplained fever</td>
</tr>
<tr>
<td>Hyponatremia, hyperkalemia, azotemia, hypercalcemia, eosinophilia</td>
</tr>
<tr>
<td>Hyperpigmentation or vitiligo</td>
</tr>
<tr>
<td>Other autoimmune endocrine deficiencies (hypothyroidism or gonadal failure)</td>
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abdominal surgery and minor procedures such as hand surgery or uterine curettage, and estimated cortisol secretion due to surgical stress was found to be 75–150 mg/day and 50 mg/day for major and minor surgeries, respectively. The results of this study formed the rationale for subsequent recommendations of perioperative glucocorticoid supplementation [7,20].

De Lange and Kars [5] and Khazen and El-Hussuna [6] investigated the incidence of AI following administration of stress-doses or conventional maintenance doses of glucocorticoids based on prospective and retrospective studies. The randomized controlled trials included in their meta-analysis mostly targeted minor to moderate surgery with a limited number of patients, and both meta-analyses concluded that the incidence of perioperative AI was very low [5,6]. These studies reported that patients taking less than 5–10 mg/day of prednisone did not have adverse side effect of AI, even if only the daily dose was maintained during relatively less invasive surgery [21–23].

**PHYSIOLOGICAL RATIONALE FOR PERIOPERATIVE GLUCOCORTICOID SUPPLEMENTATION**

Despite the low incidence of surgery-induced AI, several major pathophysiologic mechanisms support the necessity of glucocorticoid administration in the perioperative period.

**Vascular tone and maintenance of blood pressure**

Glucocorticoids have a permissive effect on vascular tone and maintenance of blood pressure [24]. Glucocorticoids alone do not increase blood pressure, but when administered with a vasopressor, glucocorticoids enhance vascular reactivity to vasopressors. The effect of glucocorticoid on vascular tone is exerted by inhibition of the synthesis of prostacyclin I₂ (PGI₂), a potent vasodilator, in the vascular endothelium [25]. If the inhibitory effect on vascular tone disappears due to a decrease in cortisol response, it may lead to increased production of PGI₂, vasodilation, and hypotension.

**Catecholamine synthesis and secretion**

Cortisol is involved in catecholamine synthesis and mediates the release of catecholamine from sympathetic nerve cells by directly regulating the activity of phenylethanolamine N-methyltransferase, an enzyme that catalyzes the conversion of norepinephrine to epinephrine in the adrenal medulla [26]. Cortisol also mediates catecholamine release from sympathetic cells [27].

**Myocardial contractility**

Cortisol helps the myocardium adapt to perioperative stress [28]. In animal studies, acute adrenal failure caused reduced myocardial contractility due to a decrease in the activity of myofibrillar adenosine triphosphatase, which is directly dependent on glucocorticoids [29]. In patients with hemodynamically unstable secondary AI, bolus intravenous hydrocortisone increases the stroke work index of the left ventricle [30].

**SYNTHETIC ADRENOCORTICOIDS**

All synthetic glucocorticoids are derivatives of cortisol, an endogenous glucocorticoid. Drugs used as therapeutic glucocorticoids include hydrocortisone, prednisolone, and dexamethasone (Table 2) [1]. Among these drugs, hydrocortisone, which has the same structure as cortisol, is the most commonly used synthetic glucocorticoid. Prednisone is an inactive prodrug that is activated to prednisolone by 11β-hydroxysteroid dehydrogenase after administration [31]. Synthetic corticosteroids have different glucocorticoid and mineralocorticoid activities. Table 2 shows the relative efficacy of commonly used corticosteroids compared to

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Glucocorticoid activity</th>
<th>Mineralocorticoid activity</th>
<th>Equivalent dose (mg)</th>
<th>Duration of action (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone (cortisol)</td>
<td>1</td>
<td>1</td>
<td>20</td>
<td>8–12</td>
</tr>
<tr>
<td>Prednisone</td>
<td>4</td>
<td>0.8</td>
<td>5</td>
<td>12–36</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>4</td>
<td>0.8</td>
<td>5</td>
<td>12–36</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>5</td>
<td>0.5</td>
<td>4</td>
<td>12–36</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>30–40</td>
<td>0</td>
<td>0.5–0.75</td>
<td>36–54</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>10</td>
<td>250</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>0</td>
<td>3000</td>
<td></td>
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</tbody>
</table>

Table 2. Relative Potency of Synthetic Steroids [1]
that of hydrocortisone [1]. When adrenal gland function is reduced, corticosteroids are used to replace both glucocorticoids and mineralocorticoids. Therefore, in patients with primary AI in which mineralocorticoids are not secreted, dexamethasone is not appropriate and synthetic mineralocorticoids, fludrocortisone, and hydrocortisone should be administered [7]. Secondary and tertiary AI are caused by a lack of glucocorticoids, so the administration of drugs with mineralocorticoid activity may cause side effects such as dose-dependent edema, fluid retention, and hypokalemia [7]. Therefore, when a high dose of hydrocortisone of 100 mg or more is required in patients with secondary and tertiary AI, switching to a drug with a higher glucocorticoid activity ratio than that of mineralocorticoid such as methylprednisolone should be considered [24].

Side effects of prolonged administration of high dose of glucocorticoid

Continuous administration of high doses of glucocorticoids after surgery can cause unwanted side effects [31]. Glucocorticoids promote gluconeogenesis in the liver and proteolysis and adipolysis in muscles, resulting in hyperglycemia. In addition, continuous glucocorticoid administration results in sodium retention, subsequent plasma volume increase, and intensifies vasopressor response to angiotensin II and catecholamines, leading to hypertension [32]. Glucocorticoids inhibit cytokine signaling and the synthesis of matrix metalloproteinases and collagen, which play an important role in wound healing [33]. In addition, it can cause gastrointestinal bleeding and various psychiatric symptoms [7]. However, most side effects occur in proportion to the duration of glucocorticoid administration, therefore, the incidence of side effects after short-term treatment is low even with high doses.

PERIOPERATIVE STRESS-DOSE GLUCOCORTICOID

Glucocorticoids should be administered during the perioperative period because cortisol secretion in response to surgical stress may fail, resulting in AI, hemodynamic instability, and adrenal crisis. Therefore, the dose of glucocorticoid should be administered at the same level as that of normal physiological response to the surgical stress after evaluating the invasiveness of surgery and inhibition of the HPA axis [24]. If there is no suppression of the HPA axis or the requirement due to surgical stress does not exceed the maintenance dose of glucocorticoids already being taken, a perioperative stress-dose of glucocorticoid is not required unless the patient shows signs of AI [7]. However, when glucocorticoid requirement increases rapidly due to surgical stress, and the inhibition of the HPA axis is clinically important, the administration of stress doses should be considered [7,8].

Approach according to HPA axis suppression

1. Nonsuppressed HPA axis

Steroid dose and duration affect HPA axis suppression. Regardless of duration, the risk of HPA axis suppression is low if the prednisone dose taken in the morning does not exceed 5 mg/day (= methylprednisolone 4 mg/day, dexamethasone 0.5 mg/day, hydrocortisone 20 mg/day) or 10 mg of prednisone every other day. In addition, if any dose of glucocorticoid is administered for less than three weeks, the HPA axis is less likely to be suppressed. These patients do not require additional administration of glucocorticoids or tests to assess the HPA axis [7].

2. Patients with suppressed HPA axis

Patients on daily dose of prednisone exceeding 20 mg for a period of more than three weeks and patients with symptoms of Cushing syndrome who are taking glucocorticoids are at high risk of HPA axis suppression [7]. These patients should be administered perioperative supplemental glucocorticoids according to the invasiveness of surgery [7].

3. Unknown HPA axis suppression

Besides these patients, patients taking prednisone at 5–20 mg/day or equivalent doses over a period of three or more weeks may experience various ranges of HPA axis suppression depending on their age, and dosage and duration of administration [34]. Even in cases with discontinued exposure of steroids, patients who inhaled high-dose steroids or high-potency topical steroids should be tested for adrenal function preoperatively and supplemental glucocorticoids should be administered based on the results of the test. There is a risk of HPA axis inhibition when inhaled glucocorticoid fluticasone ≥ 750 μg/day (or beclomethasone ≥ 1,500 μg/day = prednisolone ≥ 10 mg/day) is administered for more than 3 weeks before surgery [35,36]. The absorption rate of topical steroids varies depending on the period of use, strength, and application site, but when
topical steroids with high potency are used for > 2 g/day for more than 2 weeks, suppression of the HPA axis may occur [37]. In addition, patients who have received three or more intra-articular or spinal glucocorticoid injections within three months prior to surgery, have symptoms of AI, or Cushing’s syndrome, the HPA axis needs to be evaluated [38].

Assessment of HPA axis suppression

1. Morning serum cortisol
   Measurement of morning serum cortisol concentrations before 8 am after stopping glucocorticoids for 24 h is a good screening test for assessing secondary and tertiary AI symptoms [39]. If the morning serum cortisol concentration is lower than 5 μg/dl, suppression of the HPA axis may be suspected and the administration of additional glucocorticoids is required [7]. If the morning cortisol concentration is greater than 10 μg/dl, it can be considered that there is no inhibition of the HPA axis, and the usual dose of glucocorticoid is taken until the day of surgery and no additional administration is required [7]. If the morning cortisol concentration is 5 to 10 μg/dl, ACTH stimulation tests are conducted, or glucocorticoids are administered based on experience.

2. Short ACTH stimulation tests
   The ACTH stimulation test determines whether adrenal function is inhibited by administering synthetic ACTH (cosyntropin 250 μg); the concentration of serum cortisol are measured 30 min after the administration of ACTH [24]. If cortisol concentration is higher than 18 μg/dl, it can be determined that proper adrenal function is maintained and additional administration of glucocorticoid is not required [7].

**RECOMMENDED DOSE OF GLUCOCORTICOID ACCORDING TO SURGICAL STRESS**

Based on recent studies, recommendations were published in *Anesthesiology* in 2017 and *Anaesthesia* in 2020 [7,8]. As presented in Table 3, Liu et al. proposed recommendations based on estimated daily cortisol secretions according to the invasiveness of surgery [7,16,17].

Recently, the Royal College of Anaesthetists and the Endocrinology Society of the United Kingdom also published guidelines in *Anaesthesia* [8], but they are different from those of Liu et al. [7]. They have similarity in that they recommend administering stress-dose steroids to patients with primary and secondary AI and HPA axis suppression. However, they recommended 100 mg of hydrocortisone for all patients undergoing minor procedures as well as major surgeries [8]. After the publication of this recommendation, when questions arose about administering the same dose for a relatively simple operation [40], the authors responded that this dose may not be appropriate for simple proce-

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Estimated cortisol secretion rate</th>
<th>Examples</th>
<th>Recommended dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial</td>
<td>8 – 10 mg/day</td>
<td>Dental surgery</td>
<td>Usual daily dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biopsy</td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>50 mg/day</td>
<td>Inguinal hernia repair</td>
<td>Usual daily dose plus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colonoscopy</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Uterine curettage</td>
<td>Hydrocortisone 50 mg IV before incision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hand surgery</td>
<td>Hydrocortisone 25 mg IV every 8 h × 24 h</td>
</tr>
<tr>
<td>Moderate</td>
<td>75 – 150 mg/day</td>
<td>Lower extremity revascularization</td>
<td>Then usual daily dose</td>
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<td></td>
<td></td>
<td>Total joint replacement</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Cholecystectomy</td>
<td></td>
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<td></td>
<td></td>
<td>Colon resection</td>
<td></td>
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<td></td>
<td></td>
<td>Abdominal hysterectomy</td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>75 – 150 mg/day</td>
<td>Esophagectomy</td>
<td>Usual daily dose plus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total proctocolectomy</td>
<td>Hydrocortisone 100 mg IV before incision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major cardiac/vascular surgery</td>
<td>Followed by continuous IV hydrocortisone 200 mg (&gt; 24 h) or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepaticojejunostomy</td>
<td>Hydrocortisone 50 mg IV every 8 h × 24 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delivery</td>
<td>Taper dose by half per day until usual daily dose reached</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trauma</td>
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IV: intravenously.
dures [41]. Therefore, we can only refer to their recommendations for major surgery. According to this guideline, for patients undergoing major surgery, hydrocortisone 100 mg or dexamethasone 6–8 mg should be administered at time of induction of anesthesia, followed by immediate initiation of a continuous infusion of hydrocortisone 200 mg/day until the patients can be administered double the pre-surgical oral dose [8].

CONCLUSION

Cortisol has a variety of critical physiological actions, and an increase in concentration due to surgical stress is important for maintaining hemodynamic stability during surgery. Although studies with more appropriate evidence are still required, evaluation of patients with possible AI and glucocorticoid administration according to surgical stress is crucial and can improve prognosis.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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INTRODUCTION

Corticosteroids are very attractive as drugs for many musculoskeletal diseases because of their potent anti-inflammatory effect. Epidural steroid injection (ESI) is widely used to treat various back pain conditions such as herniated intervertebral disc and spinal stenosis. Corticosteroids have been used to treat spinal diseases for a long time. Initially, they were delivered into intrathecal space in 1954 [1]. However, because of the transient pharmacological effect, the injection route of corticosteroids was changed into epidural space. Several studies have supported the efficacy of ESI in spinal disease [2-4]. Transforaminal epidural steroid injection (TFESI) is used to relieve pain and reduce the potential need for surgery [5,6]. Radicular pain is caused not only by mechanical compression but also due to inflammation of the affected nerve roots because the nucleus pulposus of the intervertebral disc evokes an immune reaction mediated via inflammatory molecules [7]. Thus the rationale for using corticosteroids in epidural block is established [8].

The complications associated with corticosteroid use are as many as their therapeutic effects. However, most complications related to ESI are not serious. Lee et al. [9] analyzed 52,935 ESI procedures performed in 22,059 patients and found no major adverse events. Similarly, no major adverse events were detected in another single-center study of 1,300 lumbar transforaminal epidural injections. Kang et al. [10] surveyed complications of 825 patients who were treated with dexamethasone epidurally. Forty patients (4.8%) showed systemic but minor and transient side effects of corticosteroids including facial flushing (1.5%).
urticaria (0.8%), and insomnia (0.8%). Serious complications such as adrenal insufficiency (AI), Cushing’s syndrome, neurological accidents, and osteonecrosis have been reported rarely [11,12]. Because these complications cause irreversible sequelae, pain physicians need to be cognizant of the side effects of corticosteroids and their prevention.

ESI is a valuable procedure used to treat spinal pain. Although systemic side effects of treatment with long-term oral administration of steroids are well established, the pharmacology and side effects associated with ESI are poorly understood. This review summarizes the complications of epidural steroids and techniques as well as related mechanical injury.

PHARMACOLOGIC PROPERTIES OF EPIDURAL STEROIDS

Pathophysiology of radiculopathy

Radiculopathy is caused by inflammation and the mechanical compression of the nerve root. Inflammation plays a major role in the evolution of radiculopathy [13]. Clinically, a large herniation of an intervertebral disc associated with significant neural compression may be asymptomatic, whereas severe radicular pain may exist without detectable root compression. Also, the size or shape of herniation, and eventual change in size or shape does not correlate with clinical presentation or course [14,15]. This shows the importance of inflammation in the pathophysiology of radiculopathy. The damaged structures release various inflammatory mediators, which trigger inflammatory reaction in the spine. For instance, the damaged facet joints release Bradykinin, serotonin, norepinephrine, and interleukin (IL)-1. Also, the nerve endings of the posterior longitudinal ligament, outer annulus, facet capsule, or periosteum release substance P, vasoactive intestinal peptide, and calcitonin gene-related peptide. The nucleus pulposus generates inflammatory mediators, including phospholipase A2 (PLA2), prostaglandin E2, IL-1α, IL-1β, IL-6, tumor necrosis factor, and nitric oxide, and it is well known that discogenic pain is mediated by these inflammatory mediators and neovascularization induced by chemical signaling [8,16]. PLA2 is the rate-limiting factor involved in the synthesis of arachidonic acid, which is the principal substrate in the cyclo-oxygenase and lipo-oxygenase pathways. Prostaglandins, along with other arachidonic acid byproducts, can cause or exacerbate pain mediated via inflammatory mechanisms and sensitization of peripheral nociceptors [17,18]. Among the inflamed structures, the dorsal root ganglion is more sensitive to mechanical pressure than the nerve root [16].

Rationale for the use of epidural corticosteroids in radiculopathy

The therapeutic effects of corticosteroids in radiculopathy are yet to be fully understood. Until now, several mechanisms have been proposed: inhibition of leukocyte function; alleviation of inflammatory events such as edema, fibrin deposition, capillary dilatation, leukocyte aggregation, phagocytosis, capillary and fibroblast proliferation, collagen deposition and cicatrization; inhibition of the synthesis of pro-inflammatory substances like PLA2; inhibition of the activity of lymphokines; inhibition of the display of chemotactic molecules on the surface of the endothelial cells; and minimization of endothelial injury [16]. In addition to their anti-inflammatory effects, corticosteroids may inhibit pain via suppression of ectopic discharges from injured nerves and decreased conduction in normal unmyelinated C fibers [19].

Pharmacokinetics of epidural steroids

The elimination half-life of triamcinolone acetonide 80 mg following interlaminar epidural injection is 506 ± 255 h, and the time to maximum concentration (Tmax) is $37.5 \pm 37.5$ h [20]. These pharmacokinetic properties of epidural steroids vary depending on the route of administration. The elimination half-life after oral, intravenous, intraarticular, and intravitreal injection of triamcinolone varies: oral, 2.6 h [21]; intravenous, 2.0 h [21]; intraarticular knee injection, 77–154 h [22]; and intravitreal, 446 h [23]. The differences between oral/intravenous and intraarticular/intravitreal/epidural administration of triamcinolone appear to be due to its particulate form. Interestingly, in the case of cervical interlaminar epidural injection with triamcinolone acetone 80 mg, the elimination half-life was 310 ± 212 h and $T_{\text{max}}$ was 22.8 ± 13.1 h, which was shorter than that of lumbar ESI due to the cervical epidural vasculature [24]. Current evidence suggests that more soluble glucocorticoids have shorter duration of systemic effect than less soluble glucocorticoids [25]. Intramuscular administration of dexamethasone is followed by partial absorption into the
systemic circulation and the biological half-life of dexamethasone is 5.2 ± 0.4 h [26]. Unfortunately, there has been no study on the pharmacokinetic features of epidural dexamethasone, and further research is required.

**ENDOCRINOLOGICAL COMPLICATIONS**

**HPA axis suppression, AI, and iatrogenic Cushing’s syndrome**

Glucocorticoids are synthesized in the adrenal cortex under the regulation of the HPA axis. They are produced on demand and not stored in body. The glucocorticoid synthesis is inhibited by three mechanisms. First, the rapid feedback (less than 10 min) is sensitive to changes in circulating glucocorticoids and not to the absolute levels of steroid. Second, early delayed feedback (30 min to 2 h) is associated with the suppression of adrenocorticotropic hormone (ACTH) synthesis, which is affected by the concentration of circulating glucocorticoids. Third, late delayed feedback (about a day) is related to high concentration of circulating glucocorticoids, persisting for days or weeks [27].

HPA axis suppression occurs in most of the patients who receive ESI, and most of them recover within 2–4 weeks [28–32]. This complication is likely to be asymptomatic and does not require treatment in most cases. Studies involving orally administered corticosteroids have shown that the treatment dose or duration is not correlated with the severity of HPA axis suppression and reported substantial individual variation in clinical effects depending on age and co-existing disease [33]. However, the results of ESI differed from the effects of oral corticosteroid intake. Sim et al. [30] conducted a randomized controlled trial comparing the HPA axis suppression under different dosages of epidural triamcinolone (40 mg vs. 20 mg) and showed that the HPA suppression in the triamcinolone 40 mg group (19.7 ± 3.1 days) was longer than in the group treated with triamcinolone 20 mg (8.0 ± 2.4 days), and the recovery rate of the triamcinolone 40 mg group was lower than in the triamcinolone 20 mg group (P = 0.015). However, the extent of HPA axis reduction, i.e., the difference between salivary cortisol (SC) concentration before ESI and SC concentration on day 1 after ESI was not affected by the dosage of corticosteroid [30]. The type of corticosteroid also affects the HPA axis suppression. Friedly et al. [25] reported that HPA axis suppression was more likely with longer-acting insoluble corticosteroid formulations such as methylprednisolone or triamcinolone than betamethasone and dexamethasone. However, patient demographics did not influence the duration of HPA axis suppression [25].

Secondary AI is known as a rare disease (0.00015–0.00028%) [34]. Its mortality is two-fold higher than in general population, which is associated with infection or adrenal crisis [34]. The common symptoms of AI are fatigue, loss of appetite, weight loss, nausea, vomiting, abdominal pain, and muscle and joint pain, which are nonspecific and therefore do not facilitate easy diagnosis. Moreover, specific symptoms such as hyperpigmentation, salt craving, and postural hypotension are uncommon in AI induced with exogenous glucocorticoids because of intact mineralocorticoid axis [35]. Therefore, an early diagnosis of iatrogenic AI is challenging for physicians. Park et al. reported that 11.8% of patients who were treated with long-term ESI beyond 6 months developed secondary AI, although they did not show AI symptoms [28]. The average number of ESIs per year in the AI group was 7.7 ± 1.3/yr and in the Non-AI group was 7.4 ± 3.3/yr.

The risk of iatrogenic Cushing’s syndrome after ESI is unknown. No well-controlled study about its incidence after ESI is available, and only several cases have been reported [36–38]. Interestingly, a few cases were associated with ritonavir treatment of patients with human immunodeficiency virus [37,38]. Park et al. [28] reported that none of the 18 subjects who were treated long-term with ESI beyond 6 months manifested iatrogenic Cushing’s syndrome. The authors used the late-night salivary cortisol (LNSC) test, which is usually performed between 23:00 and 24:00, and is known to be very sensitive and specific for the diagnosis of Cushing’s syndrome [39]. Sim et al. [30] also conducted an LNSC test in 30 subjects who received triamcinolone acetate 40 mg or 20 mg and showed the absence of iatrogenic Cushing’s syndrome in either group.

**Effects on glucose metabolism & hyperglycemia**

Glucocorticoids decrease insulin sensitivity and peripheral glucose uptake as well as hepatic gluconeogenesis. Hyperglycemia may be one of the annoying side effects after ESI, especially in patients with diabetes.

In a study by Ward et al. [40], 10 healthy volunteers were administered 80 mg of triamcinolone (equivalent to dexamethasone 16 mg) via caudal ESI. Fasting insulin and glucose levels rose significantly one day after ESI and returned to normal by 1 week. In a study of patients receiving ESI or
glenohumeral joint injection, serum glucose was elevated for approximately 1 day [41]. Maillefert et al. [42] followed nine healthy subjects for 21 days after a single epidural injection of dexamethasone 15 mg and found no changes in fasting glucose. These studies dispute the hypoglycemic effect of ESIs in healthy individuals.

ESIs appear to have a greater effect on glucose control in diabetics. Diabetic patients may have significantly reduced cytochrome p450 3A4 expression and activity [43]. Thereby, a decreased clearance of glucocorticoids and increased duration of systemic side effects are observed. Gonzalez et al. [44] followed 12 patients with diabetes after epidural injection of betamethasone 12–18 mg via transforaminal and caudal route and reported statistically significant elevations in blood glucose levels in diabetic subjects. This effect peaked on the day of the injection and lasted approximately 2 days. A study of 100 patients with pre-existing diabetes by Kim et al. [45] reported that ESIs were associated with significant elevations in postprandial blood glucose in diabetic patients for up to 4 days after the procedure. The higher dose of triamcinolone increased the glucose levels greater than the lower dose regardless of pain control, employment status, or clinical outcome. Thus, they recommended lower doses in patients with diabetes [45]. Based on the above studies, the elevation in blood glucose among diabetic subjects was observed for two to three days following ESI, and therefore diabetic patients are advised to control their blood sugar levels tightly until three days after the procedure.

Effects on bone metabolism & osteoporosis

In general, corticosteroid therapy results in bone loss and osteoporosis, which could be a challenge, especially in postmenopausal women. Corticosteroids affect bone remodeling by increasing bone resorption via apoptosis of osteocytes and enhanced osteoclast activity. Many studies have investigated bone mineral density (BMD) in patients taking oral corticosteroids. However, orally administered corticosteroids exhibit different absorption characteristics and effects compared with those associated with epidural injections. Therefore, a direct comparison between the two is difficult.

Dubois et al. [46] reported the absence of a relationship between cumulative epidural steroid dose and BMD in healthy men and women pretreated with at least 3 g of methylprednisolone. However, in postmenopausal women, an ESI with triamcinolone 80 mg induced a significant decrease in hip BMD at 6 months compared with baseline (P = 0.002) and an age-matched control group (P = 0.007) [47]. Similarly, Kim and Hwang [48] reported a retrospective study in which multiple ESIs with an approximate cumulative dose of triamcinolone 400 mg reduced hip BMD in postmenopausal women. The average duration between the first and last ESIs was 34.4 ± 2.6 months. The risk of osteoporotic fracture appears to increase due to ESI. Mandel et al. [49] conducted a large retrospective cohort study comparing 3,415 patients who received at least one ESI with 3,000 patients who did not receive any ESI. ESI increased the risk of fractures by a factor of 1.21 (95% confidence interval, 1.08–1.30) after adjustment for covariates (P = 0.003). Therefore, physicians should keep in mind that ESI increases the risk of osteoporosis and fracture in postmenopausal women.

Abnormal uterine bleeding

Abnormal uterine bleeding (AUB) is not infrequent in women treated with ESI. The incidence of AUB in women (70% premenopausal and 30% postmenopausal) who received ESI was 2.5% of 8,166 ESIs [50]. However, the exact relationship between AUB and ESI was not revealed exactly and sex hormone levels after ESI have yet to be measured. In the case of intra-articular injection, corticosteroid therapy induces a temporary, but considerable suppression of sex hormone secretion [51].

IMMUNOLOGICAL/INFECTIOUS COMPLICATIONS

Immunosuppression and infection

Immunosuppression is one of the most serious side effects associated with iatrogenic corticosteroid use. Corticosteroids suppress inflammatory genes, upregulate anti-inflammatory genes, decrease the production of proinflammatory cytokines, and inhibit phagocyte function [52]. Preoperative intra-articular corticosteroid injection is associated with an increased risk of postoperative periprosthetic infection [53]. Preoperative ESI also appears to be related to infection after spine surgery. The overall rate of postoperative infection related to single-level lumbar decompression after ESI was reported to vary between 0.8% and 1.7%, which was more common within 1 month and 1–3 months
before surgery than within 3–6 months and 6–12 months before surgery [54]. Therefore, the optimal interval between the last preoperative ESI and surgery should be at least 3 months to prevent postoperative infection. Singla et al. [55] also reported similar results suggesting that preoperative ESI within 3 months of lumbar fusion was associated with an increased rate (1.6%) of postoperative infection in a retrospective cohort of 88,540 patients.

**Allergic reaction & anaphylaxis**

Despite the anti-inflammatory and anti-allergic effects of corticosteroids, no systemic hypersensitivity was detected, paradoxically [56]. The allergic reactions or hypersensitivity usually occur due to exposure to preservatives or steroids. The incidence of anaphylaxis was 0.5% in the study of patients injected with intravenous corticosteroids [57]. However, no study analyzed the incidence of anaphylaxis in patients using epidural corticosteroids except in a few cases. Most of the cases are associated with triamcinolone or methylprednisolone treatment and symptoms include sneezing, angioedema, tachycardia, marked hypotension, itching, redness, and peri-orbital edema [58–60].

Facial flushing is a common side effect of ESI, and is associated with urticaria and histamine-mediated reaction [61]. Most types of corticosteroids used in ESI cause facial flushing. Cicala et al. [61] reported that 9.3% of patients who received cervical ESI with methylprednisolone acetate manifested facial flushing. In the retrospective cohort study of Kim et al. [62], the overall incidence of facial flushing was 28% among 150 subjects who received ESI with 16 mg of dexamethasone. In this study, the female subjects were vulnerable to facial flushing (64%) and all cases of flushing were resolved within 48 h.

**MISCELLANEOUS COMPLICATIONS**

**Psychiatric complications**

Corticosteroid-induced psychiatric complications are not infrequent. Wada et al. [63] reported that corticosteroid-induced psychiatric syndrome including depression, mania, psychosis, and delirium occurred in 0.87% of 2,069 patients (15 patients with a mood disorder and 3 patients with a psychotic disorder), who showed a relatively good outcome with full remission within 1–3 months. However, the pathophysiology of this complication was not clear. Corticosteroid is suggested to affect dopaminergic or cholinergic systems, reduce serotonin release, and induce toxic effects in the hippocampus or other brain regions [64]. Most of the studies involved oral or intravenous administration of corticosteroid, but not ESI. Benyamin et al reported a case of a 67-year-old male who received multiple corticosteroid injections including ESI, and developed psychotic symptoms such as racing thoughts, anger, agitation, pressured hyper-verbal speech, and paranoia, which spontaneously resolved in 7–10 days [65].

**Ocular complications**

Corticosteroid therapy can increase intraocular pressure (IOP), which is known as steroid-induced ocular hypertension, steroid-induced glaucoma (SIG), and at worst blindness. The prevalence of SIG is not reported yet, but non-responders to corticosteroid was accounted for 61–63% (IOP elevation < 5 mmHg), moderate responders 33% (IOP elevation ranging 6 to 15 mmHg), and high responders constituted 4–6% (IOP elevation > 15 mmHg) [66]. However, these results are based on corticosteroid administration through the topical, intraocular, periocular, oral, intravenous, inhaled, nasal, and transcutaneous routes. A single case report involved a patient who experienced sudden bilateral blurred vision due to increased IOP after ESI, warranting immediate ophthalmic intervention. The symptom resolved within three and one half months [67]. In addition, a few case reports involved other ophthalmological complications such as retinal venous hemorrhage, amblyopia, transient bilateral vision defect, central serous chorioretinopathy, and subcapsular cataracts after ESI [68,69].

**Steroid-induced myopathy**

Steroid-induced myopathy is a rare complication characterized clinically by proximal lower extremity weakness, normal creatine kinase, normal electromyogram, and loss of type IIa fibers [52]. There is no research or case report on steroid-induced myopathy associated with ESI. Therefore, further research is needed to address this problem.

**Epidural lipomatosis**

A few case reports suggest epidural lipomatosis, which is characterized by excessive accumulation of unencapsulated fat in the spinal canal [70–72]. This complication is usu-
ally associated with long-term ESI and can cause symptoms of spinal cord or nerve root compression. The prognosis of epidural lipomatosis is not good. Two of the cases required spine surgery [71,72].

**MISCELLANEOUS ISSUES FOR SAFE ESI**

**Corticosteroids: particulate vs. nonparticulate steroids**

The corticosteroids for ESI are divided into particulate (triamcinolone and methylprednisolone) and nonparticulate (dexamethasone and betamethasone) formulations. Several cases of spinal cord ischemia after ESI have been reported since they were first described in 2002 by Houten and Errico [73]. Reports of spinal cord ischemia, paralysis, permanent blindness, and death after ESI have raised concerns about the potential embolization of particulate corticosteroids. Proposed mechanisms include direct injury to the spinal arteries and embolization. Specifically, the transforaminal approach entails needle insertion in close proximity to the spinal cord arteries. Inadvertent arterial injection of a particulate corticosteroid may result in embolic infarction and subsequent permanent neurologic compromise. Recent investigations demonstrate an alternative mechanism of injury. Several particulate steroids have been shown to exert immediate and massive effect on microvascular perfusion in a mouse model via formation of red blood cell (RBC) aggregates associated with the transformation of RBCs into spiculated RBCs [74,75].

However, dexamethasone does not form particles or aggregates large enough to cause an embolism, based on published case reports of paraplegia, quadriplegia, or stroke following ESI [74]. However, a mixture of dexamethasone or betamethasone and ropivacaine induced a pH-dependent crystallization in vitro [76,77]. In 2011, the Food and Drug Administration (FDA) required a label change for triamcinolone, stating that it should not be used for ESI. Nonetheless, particulate steroids continue to be used because of a theoretical advantage of pain relief secondary to delayed clearance from the spinal canal [78]. Three randomized studies investigated the effectiveness of different steroid preparations. Two studies reported no evidence that nonparticulate steroids such as dexamethasone at 10 mg were less effective than particulate steroids such as methylprednisolone, triamcinolone, or betamethasone in lumbar TFESI [79,80]. Conversely, Park et al. [81] reported that the nonparticulate steroid dexamethasone was statistically less effective than the particulate steroid in terms of pain relief. In 2020, Donohue et al. [82] reported that there was no significant difference in pain relief at any point between nonparticulate and particulate steroids and recommended the use of nonparticulate corticosteroids in ESI given the safety concerns associated with particulate corticosteroids. Considering the potential risk of catastrophic complications, nonparticulate steroid preparations should be considered as first-line agents when performing ESI. Further studies are necessary to compare corticosteroid preparations.

**Optimal interval and dosage of ESI**

Unfortunately, there is no definite consensus on what constitutes the appropriate regimen of ESIs, and little information concerning recommendations or practice guidelines is available to date. A significant variation in dose, frequency, and ESI interval was attributed to physician preference. In a survey conducted by Vydra et al. [2], most physicians (56.0%) preferred 10 mg of dexamethasone for ESI, followed by 8 mg (12%), 4 mg (9%), 15 mg (8%), 20 mg (6%), 6 mg (6%), and 12 mg (3%). Also, many of the doctors (40%) allowed 4 ESIs annually, followed by 3 (29%), 6 (17%), 5 (6%), 2 (3%), 8 (2%), 10 (2%), 9 (1%), and > 10 injections (1%) [2]. Kim et al. [83] published a survey of 122 pain centers adopting the current ESI regimen. More than half (55%) of Korean pain physicians used dexamethasone for ESIs. The minimum interval of subsequent ESIs is 3.1 weeks at academic institutions and 2.1 weeks at private pain clinics [83].

Determining the optimal steroid dose, duration, and interval for ESIs is essential to develop a treatment protocol with minimal complications without compromising the treatment effectiveness. Above all, a consensus is needed to determine the major complications associated with steroids indicating limited corticosteroid use. Rare complications, such as epidural lipomatosis, steroid-induced myopathy, and iatrogenic Cushing’s syndrome or complications that are patient-specific such as allergic reactions cannot be used as a criterion for limited ESI use. Most epidural steroid complications are associated with systemic absorption of corticosteroids, which is reflected by HPA axis suppression. The HPA axis suppression as an indicator of a ESI limitation has several advantages. First, it is observed in all patients who receive ESI [28,30–32]. Second, the recovery
curve of HPA function after ESI is similar to that of the elimination of epidurally injected steroid [20,24]. Third, it represents a dose-response relationship, which provides important information about minimal dosage of epidural steroids [30]. Finally, the recovery of HPA axis function is closely related to AI, one of the serious complications of ESI [28].

Before discussing appropriate ESI interval, physicians should consider the need to repeat ESI multiple times. Repeated ESIs within 3 months provide cumulative benefit [84]. If multiple ESIs are considered, an appropriate interval between ESIs should be decided based on the average duration of HPA axis suppression after ESI without affecting the physiological restoration. Another rationale for an appropriate interval is to wait until the peak effects of epidural steroid treatment are detected to avoid needless additional ESI [85]. Chon and Moon [31] reported that the HPA axis suppression period after ESI with triamcinolone 40 mg was 19.9 ± 6.8 days, which was similar to that of Sim et al. [30] (19.7 ± 3.1 days). Accordingly, the minimum recommended interval between ESIs using triamcinolone 40 mg might be 3 to 4 weeks for safety. The HPA axis suppression period is affected by the dose of epidural steroid administered. In the study of Sim et al. [30], the HPA suppression period after the epidural injection of triamcinolone 20 mg was 8.0 ± 2.4 days. Therefore, the smaller the dose of epidural steroid, the closer is the ESI minimum interval. The type of corticosteroid also affects the duration of HPA axis suppression. Friedly et al. [25] reported that particulate corticosteroids such as methylprednisolone and triamcinolone showed relatively longer HPA axis suppression than the non-particulate forms like betamethasone and dexamethasone. In the case of methylprednisolone and triamcinolone, the HPA suppression lasted an average of 3 weeks; however, the serum cortisol concentrations following 3-week treatment with betamethasone and dexamethasone was not significantly different from the control group. Similarly, Chutatape et al. [86] reported that epidural dexamethasone 8 mg decreased both ACTH and serum cortisol concentrations below 7 days. These results may be associated with the characteristics of the particulate steroid formulations, suggesting that long-acting and insoluble types can cause sustained systemic absorption of the corticosteroid. In summary, multiple ESIs using particulate steroid require sufficient interval of about 3–4 weeks because of long-lasting HPA axis suppression, while non-particulate steroids require shorter periods.

The types of corticosteroids, treatment effectiveness and duration, and the incidence of complications should be considered to determine the optimal dosage of ESI. In the case of oral corticosteroid intake, a multidisciplinary European League Against Rheumatism (EULAR) task force group of experts recommended that the risk of long-term corticosteroid therapy depended on dosage: treatment with less than 5 mg prednisone equivalent per day had low risk, whereas patient-specific characteristics should be considered between 5 mg and 10 mg/day, and levels greater than 10 mg/day could increase the risk of harm [87]. However, in the case of ESI, it is controversial whether there is a relationship between systemic complications and the dosage of corticosteroids. Habib et al. [88] conducted a randomized, single-blind, controlled trial that showed no significant difference between the two ESI doses of methylprednisolone (80 mg and 40 mg) in terms of the rate of secondary AI (P = 0.715) at 3 weeks, except for the visual analog scale (VAS) (P = 0.049) at 3 weeks. However, in the double-blind, randomized controlled trial of Sim et al. [30], there was a significant difference between ESIs with 40 mg and 20 mg doses of triamcinolone in terms of HPA suppression period (19.7 ± 3.1 days vs. 8.0 ± 2.4 days, P = 0.0005) and the slope in the linear mixed-effects model denoting the recovery rate of HPA axis (0.00431 ± 0.00043 vs. 0.00647 ± 0.00069, P = 0.015) at 4 weeks. However, there were no differences in VAS (P > 0.99) and AI incidence (P = 0.220) at 4 weeks between the two groups in Sim’s study.

The World Institute of Pain (WIP) Benelux working group recommended that the number of ESIs should be adjusted according to the clinical response, suggesting that a 2-week interval for additional ESI may be appropriate for proper evaluation and minimization of endocrine side effects, and the lowest effective dose should be used for ESI (40 mg for methylprednisolone, 10 to 20 mg for triamcinolone acetate, and 10 mg for dexamethasone phosphate) [68].

**ESI for a pregnant or breastfeeding patient**

Approximately 50% of pregnant women experience low back pain. Despite its prevalence, low-back pain (LBP) in pregnancy is considered normal by many patients and physicians. Also, safe treatment options in pregnancy are still disputed. Concerns regarding maternal and fetal well-being restrict the use of interventional treatment regimens by pain physicians, resulting in a higher incidence of obstetric complications.
Sehmbi et al. [89] reviewed 56 studies investigating management strategies for LBP in pregnancy. According to this review, three case reports involved ESI to alleviate symptoms of LBP, but all pregnant patients eventually required operative intervention due to recurrence or progression of neurological symptoms. In brief, there is weak evidence supporting the analgesic and surgery-delaying effect of ESI in pregnant patients with LBP, which is consistent with observations involving non-pregnant patients. Although a single dose of epidural steroid appears to be associated with a low risk to the fetus, it is recommended that ESI should be reserved for pregnant patients with new onset of signs or severe symptoms of lumbar nerve root compression before surgery.

The use of ESI during breastfeeding has yet to be investigated comprehensively. The secretory function of prolactin in humans is sensitive to changes in the activity of the HPA axis in a dose-dependent manner [90]. McGuire reported a case of 35-year-old mother treated with ESI and facet joint injection with triamcinolone 80–120 mg resulting in temporary reduction of lactation [91]. Although a detailed study is needed, patients should be informed that the amount of breast milk may decrease from day 3 to day 9 after ESI. Karahan et al. [92] reported that methylprednisolone concentrations in breast milk and maternal serum following high-dose (1,000 mg) methylprednisolone IV pulse therapy showed a similar trend at all time points. Eight hours after the injection, the concentrations of methylprednisolone in the milk and maternal serum were low; the transfer of methylprednisolone into breast milk is low. They recommended that mothers need to wait for 2–4 h to further limit the level of exposure although the risk to the infant seems low. Currently, no information on the effect of epidural steroids on breast milk or breastfed infants is available.

CONCLUSIONS

The complications caused by epidural corticosteroids are relatively rare and rarely serious. However, pain physicians should be aware of the complications because a growing number of patients with various diseases are treated with ESI. Although the relationship between the degree of systemic absorption and the side effects of ESI are not well known, and most ESI-related complications appear to be associated with systemic absorption of corticosteroids. Thus, the complications of ESI differ from those administered via oral or venous routes and depend on the type of steroids used. The duration of HPA axis suppression adequately reflects the systemic absorption of epidural corticosteroids. In terms of safety, non-particulate steroids are preferred over particulate steroids. The ESI interval should be at least 3–4 weeks for a particulate steroid, but non-particulate steroids may be administered more frequently. The ESI dosage is controversial and should be designed to minimize HPA axis suppression for each drug.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Pharmacological strategies to prevent postoperative delirium: a systematic review and network meta-analysis

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Background: Postoperative delirium (POD) is a condition of cerebral dysfunction and a common complication after surgery. This study aimed to compare and determine the relative efficacy of pharmacological interventions for preventing POD using a network meta-analysis.

Methods: We performed a systematic and comprehensive search to identify and analyze all randomized controlled trials until June 29, 2020, comparing two or more pharmacological interventions, including placebo, to prevent or reduce POD. The primary outcome was the incidence of POD. We performed a network meta-analysis and used the surface under the cumulative ranking curve (SUCRA) values and rankograms to present the hierarchy of the pharmacological interventions evaluated.

Results: According to the SUCRA value, the incidence of POD decreased in the following order: the combination of propofol and acetaminophen (86.1%), combination of ketamine and dexmedetomidine (86.0%), combination of diazepam, flunitrazepam, and pethidine (84.8%), and olanzapine (75.6%) after all types of anesthesia; combination of propofol and acetaminophen (85.9%), combination of ketamine and dexmedetomidine (83.2%), gabapentin (82.2%), and combination of diazepam, flunitrazepam, and pethidine (79.7%) after general anesthesia; and ketamine (87.1%), combination of propofol and acetaminophen (86.0%), and combination of dexmedetomidine and acetaminophen (66.3%) after cardiac surgery. However, only the dexmedetomidine group showed a lower incidence of POD than the control group after all types of anesthesia and after general anesthesia.

Conclusions: Dexmedetomidine reduced POD compared with the control group. The combination of propofol and acetaminophen and the combination of ketamine and dexmedetomidine seemed to be effective in preventing POD. However, further studies are needed to determine the optimal pharmacological intervention to prevent POD.

Keywords: Delirium; Network meta-analysis; Pharmacology; Surgical procedures, operative.
INTRODUCTION

Postoperative delirium (POD) is a condition of cerebral dysfunction and a common complication after surgery that occurs in 15–35% patients [1]. Old age, a history of stroke, use of narcotic analgesics, poor physical condition, alcoholism, preexisting cognitive impairment, and type of surgery are known risk factors for POD [2,3]. Especially patients undergoing major surgery, including cardiac surgery, are at increased risk of developing POD because of the complexity of the surgical procedure, the administration of intraoperative and postoperative anesthetic and other pharmacological agents. For this reason, POD is reported to affect up to 57% of cardiac-surgery patients [4].

POD is characterized by altered consciousness, disorientation, impaired memory, perceptual disturbance, altered psychomotor activity, and altered sleep-wake cycles after surgery. POD increases the rate of mortality, length of hospital stay, risk of placement to long-term care institutions, or functional disability, thus increasing hospitalization costs [2,5]. Therefore, appropriate prevention and treatment of POD is important for enhancing postoperative recovery and quality of life in elderly patients [6].

The treatment strategies for POD are well organized compared to the prevention strategies. The treatment for POD includes treating the underlying cause; correcting fluid and electrolyte imbalance or hypoxia; removing catheters if present, and treating patients who are restless, agressive, agitative, and harm to themself or others with antipsychotics such as haloperidol, chlorpromazine, olanzapine, and risperidone [7,8].

However, it is unclear which strategies are effective for preventing POD. Therefore, various strategies to prevent POD, especially variable pharmacological interventions, such as dexmedetomidine, propofol, midazolam, ketamine, and acetaminophen, have been applied and compared. However, each study only compared two or three drugs and reported diverse results.

Recently, a few systematic reviews and meta-analyses have demonstrated and integrated the preventive effect of various interventions [9–14]. However, each study was limited to pair-wise meta-analysis and examined only two pharmacological interventions. No previous network meta-analysis (NMA) has compared the effectiveness of all available pharmacological interventions. Further, the aforementioned studies included studies conducted prior to 2017.

NMA complements traditional pair-wise meta-analysis by combining direct and indirect comparisons of treatments and provides objective ranking of various treatments based on the corresponding surface under the cumulative ranking curve (SUCRA) [15].

Thus, we reviewed all articles that investigated the effectiveness of pharmacological interventions to prevent POD and performed NMA to compare and quantify the rank order of the effectiveness of pharmacological interventions to prevent POD.

MATERIALS AND METHODS

Protocol and registration

We developed the protocol for this systematic review and NMA according to the preferred reporting requirements for systematic review and meta-analysis protocol (PRISMA-P) statement [16]. We registered the review protocol at the International Prospective Register of Systematic Reviews (registration no. CRD42020189363; www.crd.york.ac.uk/prospero) on May 7, 2020.

This systematic review and NMA of pharmacological interventions for preventing POD were performed according to the protocol recommended by the Cochrane Collaboration [17] and reported according to the PRISMA extension for NMA guidelines [18].

Search strategy

We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar from inception to June 29, 2020 using the search terms related to pharmacological interventions for preventing POD. The search terms used for MEDLINE and EMBASE are presented in Supplementary Material. Two investigators (GJC and HK) screened the titles and abstracts of the retrieved articles. Reference lists were imported to Endnote software 8.1 (Thompson Reuters, USA), and duplicate articles were removed. Additionally, the references of articles obtained from the original search were reviewed to identify relevant articles.

Inclusion criteria and exclusion criteria

We included only randomized controlled trials (RCTs) that compared two or more pharmacological interventions
to prevent POD.

The PICO-SD information included the following:

1. Patients (P): all patients receiving surgery under general or regional anesthesia
2. Intervention (I): pharmacological interventions to prevent POD
3. Comparison (C): other pharmacological interventions to prevent POD, placebo, or no treatment
4. Outcome measurements (O): the incidence of POD
5. Study design (SD): RCTs
6. Subgroup analysis: general anesthesia and cardiac surgery

Exclusion criteria contained the following features:

1. Review articles, case reports, case-series, letters to the editor, commentaries, proceedings, laboratory science studies, and all other non-relevant studies
2. Studies that failed to report the outcomes of interest
3. Studies that investigated the effect of inhalational anesthetics or patient-controlled analgesia (PCA) regimens

There was on language limitations or date restrictions in our study.

Study selection

Two reviewers (JML and YJC) independently screened the titles and abstracts of the studies to identify trials that met the inclusion criteria outlined above. For articles determined to be eligible based on the title and/or abstract, the full paper was retrieved. Potentially relevant studies chosen by at least one author were retrieved, and the full text was evaluated. Full-text articles were assessed separately by two authors (JML and YJC), and any disagreements were resolved through discussion. In cases where agreement could not be reached, the dispute was resolved with the help of a third investigator (HK). To minimize data duplication owing to multiple reporting, articles from the same author, organization, or country were compared.

Data extraction

Using a standardized extraction form, the following data were extracted independently by two investigators (JML and YJC): 1) title, 2) name of the first author, 3) name of the journal, 4) year of publication, 5) study design, 6) type of pharmacological interventions, 7) dose of pharmacological agents, 8) country, 9) risk of bias, 10) inclusion criteria, 11) exclusion criteria, 12) age, 13) number of subjects, and 14) incidence of POD.

If the information was inadequate, attempts were made to contact the study authors, and additional information was requested. If unsuccessful, missing information was calculated from the available data, if possible, or was extracted from the figure using the open source software Plot Digitizer (version 2.6.8; http://plotdigitizer.sourceforge.net).

The reference lists were divided into two halves. Two investigators completed data extraction, one for each half of the reference list. Data extraction forms were cross-checked to verify the accuracy and consistency of the extracted data.

The degree of agreement between the two independent data extractors was computed using kappa statistics to measure the difference between the observed and expected agreements, i.e., whether they were random or by chance. Kappa values were interpreted as: 1) less than 0: less than chance agreement; 2) 0.01 to 0.20: slight agreement; 3) 0.21 to 0.40: fair agreement; 4) 0.41 to 0.60: moderate agreement; 5) 0.61 to 0.80: substantial agreement; and 6) 0.8 to 0.99: almost perfect agreement [19].

Risk of bias assessment

The quality of the studies was independently assessed by two investigators (JML and YJC) using the Revised Cochrane risk of bias tool for randomized trials (RoB 2.0). Risk of bias judgment was assessed in the following domains: bias arising from the randomization process, bias due to deviations from intended intervention, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported results. Based on the results of risk of bias judgment, formal overall risk of bias judgment was categorized as “low risk of bias,” “some concern,” and “high risk of bias” [20].

Statistical analysis

Ad-hoc tables were designed to summarize data from the included studies by showing their key characteristics and any important questions related to the review objectives. After extracting the data, the reviewers determined the feasibility of a meta-analysis.

A multiple treatment comparison NMA is a meta-analysis generalization method that includes both direct and in-
Pharmacological strategies for POD

direct RCT comparison of treatments. A random-effects NMA based on a frequentist framework was performed using STATA software (version 15, StataCorp LP, USA) based on mvmeta with NMA graphical tools developed by Chaimani et al. [21].

Before conducting the NMA, we evaluated the transitivity assumption by examining the comparability of the risk of bias (all versus removing high risks of bias from the randomization process and overall risk of bias), demographics, and types of pharmacological interventions as potential treatment-effect modifiers across comparisons.

A network plot linking the included pharmacological interventions to prevent POD and their combination with other pharmacological agents was formed to indicate the types of agents, number of patients on different agents, and the level of pair-wise comparisons. The nodes show comparisons of pharmacological agents being compared, and the edges show the available direct comparisons among the pharmacological agents. The nodes and edges are weighted on the basis of the weights applied in NMA and the inverse of the standard error of effect.

We evaluated the consistency assumption for the entire network using the design-by-treatment interaction model. We also evaluated each closed loop in the network to evaluate local inconsistencies between the direct and indirect effect estimates for the same comparison. For each loop, we estimated the inconsistency factor (IF) as the absolute difference between the direct and indirect estimates and 95% confidence interval (CI) for each paired comparison in the loop [22]. When the IF value with 95% CI started at 0, it indicated that the direct evidence and the indirect evidence were consistent.

Mean summary effects with CI were presented together with their predictive intervals (PrIs) to facilitate interpretation of the results considering the magnitude of heterogeneity. PrIs provide an interval that is expected to encompass the estimate of a future study.

A rankogram and a cumulative ranking curve were drawn for each pharmacological intervention. Rankogram plots are the probabilities for treatments to assume a possible rank. We used surface under the cumulative ranking curve (SUCRA) values to present the hierarchy of pharmacological interventions to prevent the incidence of POD. The SUCRA is a relative ranking measure that accounts for the uncertainty in the treatment order, that is, accounts for both the location and the variance of all relative treatment effects. A higher SUCRA value is regarded as a more positive result for individual interventions [23].

We performed subgroup analysis based on all types of anesthesia, general anesthesia, and cardiac surgery, because the incidence of POD is expected to be different according to the type of anesthesia, and increase after cardiac surgery.

Quality of evidence

The evidence grade was determined using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system, which uses a sequential assessment of the evidence quality, followed by an assessment of the risk-benefit balance and a subsequent judgment on the strength of the recommendations [24].

RESULTS

Study selection

We initially retrieved 235 articles from MEDLINE, EMBASE, CENTRAL, and Google Scholar databases and 17 articles through a manual search. After adjusting for duplicates, 245 studies remained. Of these, 182 studies were discarded after reviewing the title and abstracts for the following reasons: related to other topics, designed as systematic reviews, reviews or retrospective studies, and conference abstracts. The full texts of the 63 remaining studies were reviewed in detail; 12 studies were excluded for the following reasons: three were study protocols [25–27], two were editorials [13,28], four were systematic reviews, [9–12] and three did not report the outcome of our interest (two compared an inhalational agent [13,29] and one was compared in the PCA regimen [30]). Thus, 51 studies with a total of 22,565 patients that included 18 different pharmacological interventions were included in this NMA (Fig. 1). The kappa value for the selected articles between the two reviewers was 0.844.

Characteristics of the included studies

The characteristics of the 51 studies are summarized in Table 1. All the studies were performed on adults with American Society of Anesthesiologists physical status classifications I, II, and III. The 51 studies were conducted in various countries, such as Australia [31,32], Canada [33,34], China [1,2,6,35–47], Denmark [48], Greece [49], India

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[50,51], Iran [52,53], Japan [54–57], the Netherlands [58–61], South Korea [62,63], Switzerland [64], Taiwan [65,66], Thailand [67], the United Kingdom [68], the United States of America [4,69–76], and Saudi Arabia [77].

Twenty-seven types of pharmacological agents, including dexmedetomidine (Dexm) [2,4,6,31,33,35,36,38–45,47, 50,51,62,63,65,66,69,70], propofol (Prop) [4,33,42–44, 47,51,66,70], acetaminophen (AAP) [70], midazolam (Mida) [4,6,77], remifentanil (Remi) [62], morphine (Morp) [31], methylprednisolone (MPDL) [32,34,48], melatonin (Mela) [58,77], dexamethasone (Dexa) [52,59,61], haloperidol (Hal) [37,54,55,60], rivastigmine (Riva) [64], ketamine (Keta) [39,71], olanzapine (Olan) [72], gabapentin (Gaba) [73,76], nimodipine (Nimo) [1], cyproheptadine (Cypr) [53], ondansetron (Onda) [49], risperidone (Risp) [67], L-tryptophan(L-tyr) [74], donepezil (Done) [68,75], Yokukansan (TJ-54) [56], diazepam (Diaz) [57], flunitrazepam (Flun) [57] and pethidine (Peth) [57], parecoxib (Pare) [46], and clonidine (Clon) [77] were evaluated.

The types of surgery investigated included cardiovascular surgery [4,31–35,42,43,47,50–52,59,61,62,64,66,70,71], orthopedic surgery [1,2,6,39,40,44,46,48,49,54,58,60,68,72,73,75–77], thoracoscopic and pulmonary surgery [41,56,65,74], abdominal and laparoscopic surgery [54–57,63,66], vascular and urology surgery [74], free flap [38], oral cancer surgery [45], and non-cardiac surgery [36,37,53,69]. The anesthesia method in the studies included only general anesthesia [1, 2,4,6,31–35,38,39,41–43,45,47,49–52,55–57,59,61–67,69– 71,76], general anesthesia + regional anesthesia [36,37,48, 54,72–74], type of anesthesia were not decribed [40,53,58, 60,68,75], and only regional anesthesia [44,46,77].

Fig. 1. PRISMA flowchart of included and excluded trials. PRISMA: preferred reporting requirements for systematic review and meta-analysis, NMA: network meta-analysis.

Study quality assessment

The risk of bias assessment in the included studies using the Cochrane tool is presented in Table 2.

All types of anesthesia

A total of 51 studies (22,565 patients) measured the incidence of POD. The pooled overall incidence of POD after all types of anesthesia was 18.5% (95% CI: 16.2% to 21.0%, $P_{\chi^2} = 0.001$, $I^2 = 92.0\%$). The network plot of all eligible comparisons for this endpoint is depicted in Fig. 2A.

Although all 27 management modalities (nodes) were connected to the network, two comparisons (Control [Cont], Dexm) were compared directly to the other 25 nodes.

The evaluation of the network inconsistency using the design-by-treatment interaction model suggested no significant inconsistency ($\chi^2 [8] = 13.37, P = 0.100$). Of the 14 closed loops in the network for the comparison of postoperative delirium, four loops (Dexm-Dexam + AAP-pro + AAP [01-04-05] [70], Dexm-Keta-Keta + Dexm [01-09-22] [39], Pro-Dexam + AAP-Prop + AAP [03-04-05] [70], Mida-Mela-Clon [06-11-25] [77]) were formed only by multi-arm trials. Thus, local inconsistency was evaluated in 10 loops. Although most loops showed no relevance in the local inconsistency between the direct and indirect point estimates,
Table 1. The Characteristics of the Including Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Surgery</th>
<th>Anesthesia</th>
<th>Assessment tool</th>
<th>Assessor</th>
<th>Management</th>
<th>Administration time</th>
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<th>Age (yr)</th>
<th>Sex, M/F (%)</th>
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<td>Noncardiac surgery</td>
<td>G/A</td>
<td>CAM, CAM-ICU, MMSE</td>
<td>Trained lay interviewers</td>
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<td>Intraop</td>
<td>147</td>
<td>74</td>
<td>49/51</td>
</tr>
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<td>Canada</td>
<td>Cardiac surgery</td>
<td>G/A</td>
<td>CAM, CAM-ICU</td>
<td>Tester</td>
<td>Dexmedetomidine Propofol</td>
<td>Postop</td>
<td>91</td>
<td>72.7</td>
<td>75/25</td>
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<td>Susheela et al. [70]</td>
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<td>USA</td>
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<td>CAM, MMSE</td>
<td>Research members</td>
<td>Dexmedetomidine Dexmedetomidine + AAP Propofol Propofol + AAP</td>
<td>Intraop &amp; Postop</td>
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<td>CAM-ICU</td>
<td>Medical staff and non-psy- psychiatrists</td>
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<td>350 No described (&gt; 65)</td>
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<td>CAM, MMSE, CDT</td>
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### Table 2. Risk of Bias Assessment

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inconsistencies were observed between the direct and indirect point estimates in the Cont-Mela-Clon (02-11-25) and Cont-Mida-Mela (02-06-11) loops (Fig. 3A).

Dexm showed a lower incidence of POD than Cont only in terms of 95% CI. Olan showed marginal significance compared with Cont in terms of 95% CI (Fig. 4A). Insignificance in the 95% PrIs suggests that any future RCT could change the significance of the effectiveness of these comparisons.

The rankograms showed that Prop+AAP and Keta+Dexm had the lowest incidence of POD (Fig. 5A). The cumulative ranking plot was drawn, and the SUCRA probabilities of the different pharmacological agents for POD were calculated (Fig. 6A). The expected mean rankings and SUCRA values of each pharmacological intervention are presented in Fig. 7A. According to the SUCRA value, the incidence of POD was lower in the order of the Prop + AAP (86.1%), followed by Keta + Dexam (86.0%), Diaz + Flun + Pethi (84.8%), and Olan (75.6%). The comparison-adjusted funnel plots showed that the funnel plots were symmetrical around the zero line, which suggested a less likely publication bias (Fig. 8A).

**General anesthesia**

A total of 35 studies (17,241 patients) were analyzed. The pooled overall incidence of POD after general anesthesia was 16.5% (95% CI: 14.2% to 19.2%, $P_{\chi^2} < 0.001$, $I^2 = 89.3\%$).

The network plot of all eligible comparisons for this endpoint is depicted in Fig. 2B. Although all 20 management modalities (nodes) were connected to the network, two comparisons (Cont, Dexam) were directly compared to the other 18 nodes.

The evaluation of the network inconsistency using the design-by-treatment interaction model suggested no significant inconsistency ($\chi^2 [6] = 11.50, P = 0.074$). Of the 10 closed loops in the network for the comparison of postoperative delirium, three loops (Dexam-Dexam + AAP-Prop + AAP [01-04-05] [70], Pro-Dexam + AAP-Prop + AAP [01-09-19] [70], Dexam-Keta-Dexam + Keta [03-04-05] [39]) were formed only by multi-arm trials. Thus, local inconsistency was evaluated in seven loops. There was no significance in the local inconsistency between the direct and indirect point estimates (Fig. 3B).

Dexm showed a lower incidence of POD than Cont only in terms of 95% CI (Fig. 4B). Insignificance in the 95% PrIs suggests that any future RCT could change the significance
Fig. 3. Inconsistency plot between the direct and indirect effect estimates for the same comparison. Inconsistency factor (IF) as the absolute difference with 95% confidence interval (CI) between the direct and indirect estimates for each paired comparison is presented. IF values close to 0 indicate that the two sources are in agreement. (A) All type of anesthesia, (B) general anesthesia, (C) cardiac surgery.

Fig. 4. Predictive interval plots between each management modality and placebo group. Diamond shape represents the mean summary effects. Black line represents the 95% confidence interval (CI), and red line represents the predictive interval (PrI). PrIs provide an interval that is expected to encompass the estimate of a future study. (A) All type of anesthesia, (B) general anesthesia, (C) cardiac surgery.
Fig. 5. Rankogram. Profiles indicate the probabilities for treatments to assume any of the possible ranks. It is the probability that a given treatment ranks first, second, third, and so on, among all of the treatments evaluated in the NMA. (A) All type of anesthesia, (B) general anesthesia, (C) cardiac surgery. NMA: network meta-analysis.

Fig. 6. Cumulative ranking curve plot. The profile indicates the sum of the probabilities from those ranked first, second, third, and so on. A higher cumulative ranking curve (surface of under cumulative ranking curve [SUCRA]) value is regarded as an improved result for an individual’s intervention. When ranking treatments, the closer the SUCRA value is to 100%, the higher the treatment ranking is relative to all other treatments. (A) All type of anesthesia, (B) general anesthesia, (C) cardiac surgery.
Pharmacological strategies for POD

Fig. 7. Expected mean ranking and surface of under cumulative ranking curve (SUCRA) values. X-axis corresponds to expected mean ranking based on SUCRA value, and Y-axis corresponds to SUCRA value. (A) All type of anesthesia, (B) general anesthesia, (C) cardiac surgery.

of the effectiveness of these comparisons.

The rankogram showed that Prop + AAP, Keta + Dexm, and Gaba had the lowest incidence of POD (Fig. 5B). The cumulative ranking plot was drawn, and the SUCRA probabilities of the different pharmacological agents for the POD were calculated (Fig. 6B). The expected mean rankings and SUCRA values of each pharmacological agent are presented in Fig. 7B. According to the SUCRA value, the incidence of POD was lower in the order of the Prop + AAP (85.9%), followed by Keta + Dexm (83.2%), Gaba (82.2%), and Diaz + Flun + Pethi (79.7%).

Cardiac surgery

A total of 19 studies (15,090 patients) were analyzed. The pooled overall incidence of POD after cardiac surgery was 15.4% (95% CI: 12.8% to 18.4%, \( P_{\text{hi}}^2 < 0.001, I^2 = 89.8\%\)).

The network plot of all eligible comparisons for this endpoint is depicted in Fig. 2C.

Although all 13 management modalities (nodes) were connected to the network, three comparisons (Cont, Dexm, Prop) were compared directly to the other 10 nodes.

The evaluation of the network inconsistency using the design-by-treatment interaction model suggested no significant inconsistency \( (\chi^2[2] = 4.12, P = 0.128) \). Of the five closed loops in the network of the comparison of postoperative delirium, two loops (Dexm-Dexm + AAP + Prop + AAP [01-04-05] [70] and Pro-Dexm + AAP-Prop + AAP [03-04-05] [70]) were formed only by multi-arm trials. Thus, local inconsistency was evaluated in three loops. There was no significance in the local inconsistency between the direct and indirect point estimates (Fig. 3C).

None of the regimens showed a lower incidence of POD than Cont only in terms of both 95% CI and 95% PrIs (Fig. 4C). The rankogram showed that Prop + AAP and Keta had the lowest incidence of POD (Fig. 5C). The cumulative ranking plot was drawn, and the SUCRA probabilities of the different pharmacological interventions for the POD were calculated (Fig. 6C). The expected mean rankings and SUCRA values of each pharmacological intervention are
presented in Fig. 7C. According to the SUCRA value, the incidence of POD was lower in the order of Keta (87.1%), Prop + AAP (86.0%), followed by Dexm + AAP (66.3%). The comparison-adjusted funnel plots showed that the funnel plots were symmetrical around the zero line, which suggested a less likely publication bias (Fig. 8C).

Quality of evidence

Three outcomes were evaluated using the GRADE system. For each outcome, the qualities of inconsistency, indirectness, imprecision and publication bias were assessed as not serious, but qualities of risk of bias were assessed as serious. Thus, the overall quality of evidence for each outcome was downgraded and rated as moderate (Table 3).

DISCUSSION

There are various pharmacological interventions to prevent POD. We performed a network meta-analysis to compare the effectiveness of reported pharmacological interventions. In our study, the incidence of POD was decreased in the following order: Prop + AAP, Keta + Dexm, Gaba, and Diaz + Flun + Pethi after all types of anesthesia; Prop + AAP, Keta + Dexm, Gaba, and Diaz + Flun + Pethi after general anesthesia; and Keta, Prop + AAP, and Dexm + AAP after cardiac surgery. However, only the Dexm group showed a statistically lower incidence of POD compared with the control group after all types of anesthesia and after general anesthesia.

In our study, there was a synergistic effect when Prop was added to AAP. Although Prop + AAP failed to show statistical significance, Prop + AAP was ranked the most effective pharmacological intervention with a low incidence of POD after all types of anesthesia and after general anesthesia. Prop is a short-acting, intravenous sedative-hypnotic agent commonly used for general anesthesia and sedation. It has also been used to control other conditions such as chemotherapy-induced emesis, as an antipruritic in patients with intractable pruritus due to liver disease, as an adjuvant in alcohol withdrawal syndrome, and to treat status epilepticus and severe refractory delirium. Prop has been recently shown to have a long-term neuroprotective effect and CNS inhibition effect [78–80]. AAP is commonly used as an adjuvant analgesic. Some prior studies have indicated that AAP reduces opioid consumption and inflammation. Recently, AAP has been shown to confer central
Pharmacological strategies for POD

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<td>None</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

GRADE: grading of recommendations, assessment, development, and evaluation.

Several reports in the past few years have evaluated Keta, which is ineffective with monotherapy, when combined with Dexm becomes the most effective modality. Keta offers a potential option for treating difficult to manage hyperactive delirium [91]. Moreover, Keta is an NMDA receptor antagonist, which reduces post-ischemic neuronal cell loss in the cortex and improves neurological outcome after cerebral ischemia [92,93]. Thus, Keta may produce a prolonged effect on postoperative neurocognitive function by causing a “preconditioning-like” effect through the temporary inactivation of NMDA receptors, thereby rendering these receptors less susceptible to subsequent activation by ischemia and reperfusion injury. However, this intriguing hypothesis has not been formally tested. Keta may also confer neuroprotection by suppressing the inflammatory response after surgery [71,94].

For quality of life, which has recently attracted attention, postoperative complications of surgical patients should be prevented and treated appropriately. Among complications, POD can directly or indirectly increase postoperative morbidity and mortality in elderly patients. Delirium is not always a transient disorder; in some cases, it may be accompanied by subtle structural brain damage, leading to permanent cognitive impairment. Therefore, there is growing interest in proper preventive methods [62,68].

In our study, we focused on the incidence of POD, preventive effect of interventions, and collected pharmacological intervention data. There have been a number of preventative methods introduced in other studies, but their efficacy has not been properly compared. To compensate for this, our NMA including various pharmacological interventions. Throughout this study, we attempted to identify the most effective prevention of POD.

There are several limitations in this study. First, as with all meta-analyses, there were clinical and methodological heterogeneities regarding administration timing (for example, preoperative or intraoperative or postoperative), method (for example, bolus or continuous infusion) and dose spectrum of pharmacological interventions, and assessor of POD and assessment tool of POD. Second, in our study,
incidence of POD was used as an indicator of prevention. However, to reduce morbidity and mortality associated with POD, it is also important to reduce the severity and duration of POD. Therefore, further studies should be conducted to evaluate the effects on the severity and duration of POD. Third, the most efficacious modalities determined in the current NMA were documented to be effective in a limited number of clinical trials. Further, as our NMA was based on various single-center small-scale trials, a risk of overestimation or underestimation of true treatment effects or lack of power to discriminate the effectiveness of pharmacological interventions may be present. Therefore, further large-scale RCTs with the qualified protocol should be conducted in the future to encompass different pharmacological interventions and substantiate our findings.

Despite these limitations, the current NMA has several strengths compared to previous NMAs. First, a rigorous methodology based on a published, pre-planned protocol to provide evidence of pharmacological interventions to prevent POD was used. Second, inconsistencies among the enrolled studies were not significant, and publication bias of the enrolled studies was minimal. Third, most enrolled studies exhibited a low risk of bias, except for bias from the randomization process and bias due to deviations from intended intervention domains.

In conclusion, the NMA performed in this study has strength and meaning for comparing pharmacological interventions in the clinical efficacy of preventing POD. Dexm showed a significant decrease in the incidence of POD compared with the control group. The combination of Prop and AAP and the combination of Keta and Dexm seemed to be effective in preventing POD. However, further studies are needed to determine the optimal pharmacological intervention to prevent POD.

**SUPPLEMENTARY MATERIALS**

Supplementary data including search terms used for MEDLINE and EMBASE can be found online at https://doi.org/10.17085/apm.20079

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**CONFLICTS OF INTEREST**

No potential conflict of interest relevant to this article was reported.

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Comparison of the effect of general and spinal anesthesia for elective cesarean section on maternal and fetal outcomes: a retrospective cohort study

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Background: Anesthesia is needed to ensure both maternal and fetal safety during cesarean sections. This retrospective cohort study compared maternal and fetal outcomes between general and spinal anesthesia for cesarean section based on perioperative hemodynamic parameters (pre- and postoperative systolic blood pressure, heart rate), mean difference of hematocrit and estimated blood loss, and neonatal Apgar scores at 1 and 5 min.

Methods: Data from electronic medical records of 331 singleton pregnancies between January 2016 and December 2018 were analyzed retrospectively; 44 cases were excluded, and 287 cases were assigned to the general group (n = 141) or spinal group (n = 146).

Results: Postoperative hemodynamic parameters were significantly higher in the general group than the spinal group (systolic blood pressure: 136.8 ± 16.7 vs. 119.3 ± 12.7 mmHg, heart rate: 93.2 ± 16.8 vs. 71.0 ± 12.7 beats/min, respectively, P < 0.001). The mean difference between the pre- and postoperative hematocrit was also significantly greater in the general than spinal group (4.8 ± 3.4% vs. 2.3 ± 3.9%, respectively, P < 0.001). The estimated blood loss was significantly lower in the spinal than general group (819.9 ± 81.9 vs. 856.7 ± 117.9 ml, P < 0.001). There was a significantly larger proportion of newborns with 5-min Apgar scores < 7 in the general than spinal group (6/141 [4.3%] vs. 0/146 [0%], respectively, P = 0.012).

Conclusions: General group is associated with more maternal blood loss and a larger proportion of newborns with 5-min Apgar scores < 7 than spinal group during cesarean sections.

Keywords: Cesarean section; General anesthesia; Outcome measures; Spinal anesthesia.
nal awareness during the operation due to inadequate anesthestia, failed intubation, and respiratory complications in the mother and newborn. Many intravenous anesthetic agents injected into the mother can cross the placental barrier and enter fetal circulation and may cause sedation or respiratory depression of the newborn.

The two types of regional anesthesia used for cesarean sections are spinal and epidural anesthesia. The advantages of regional anesthesia include reduced complications associated with general anesthesia and promotion of initial bonding between the mother and the baby (because the mother is awake during the operation) [1]. Recently, spinal anesthesia has been preferred over epidural anesthesia for cesarean section because of its rapid onset, effectiveness, and lower requirement for local anesthetics; however, it is associated with a higher incidence of arterial hypotension [2]. Spinal anesthesia using small amounts of local anesthetics is less likely to cause maternal systemic toxicity or total spinal anesthesia. Therefore, it is pertinent to compare the effects of general and spinal anesthesia during cesarean sections on maternal and fetal outcomes.

Previous studies have compared postoperative maternal hematocrit (hct) levels between general and spinal anesthesia for cesarean section [3,4]. The Cochrane database [5] has three papers on maternal blood loss in relation to cesarean section; one study has compared epidural and general anesthesia and two studies have compared spinal and general anesthesia.

The Apgar score is an indicator of neonatal well-being. Several studies have reported no significant difference in Apgar scores between general and regional anesthesia [5], but two studies [6,7] reported that the 1-min Apgar scores were lower in general than regional anesthesia. Thus, controversy remains regarding the association of neonatal well-being scores with general and regional anesthesia.

This retrospective study reviewed the medical records of women who underwent cesarean section under general anesthesia or spinal anesthesia and compared the maternal and fetal outcomes based on perioperative hemodynamic parameters (pre- and postoperative systolic blood pressure, heart rate), hematocrit, and estimated blood loss and neonatal Apgar scores at 1 and 5 min between both anesthesia groups.

**MATERIALS AND METHODS**

This study was approved by our ethics committee/Institutional Review Board (no. KYUH 2019-04-008) and registered at the Korea Clinical Research Information Service (http://cris.nih.go.kr; no. KCT 0004783). The need for informed consent was waived because of the retrospective study design. We retrospectively analyzed data from 331 singleton deliveries that occurred between January 2016 and December 2018; data regarding maternal and fetal outcomes after general or spinal anesthesia for elective cesarean section were analyzed and compared. Two anesthesiologists were in charge of anesthesia during the obstetric surgeries. Both anesthesiologists induced anesthesia using the same anesthetic agents; patient monitoring, extubation criteria, and the same spinal technique were performed according to our institutional protocol.

All subjects were scheduled for elective cesarean section, with their physical condition classified according to the American Society of Anesthesiologists class 2, since American Society of Anesthesiologists categorizes “pregnancy” as class 2. Exclusion criteria included the need for emergency or epidural anesthesia, conversion from spinal to general anesthesia, and deliveries wherein bleeding was anticipated, such as placenta previa or coagulopathy. In total, 44 of the 331 subjects were excluded. The remaining 287 subjects were classified into either general anesthesia (n = 141) or spinal anesthesia (n = 146) groups (Fig. 1). The anesthesia induction method was dependent on the mother’s choice, and the difference in preference between the two anesthesiologists were recorded.

All parturient women fasted for at least 8 h preoperatively and were not administered any pharmacological premedication. In the operating room, we routinely used standard monitoring, including electrocardiography, noninvasive blood pressure, and pulse oximetry (SpO₂).

In the general anesthesia group, for all patients, we used...
the bispectral index (BIS) and preoxygenation using 100% oxygen delivered over 3–5 min. Subsequently, anesthesia was induced with 5 mg/kg of thiopental. Intravenous injection of 0.5 mg/kg rocuronium facilitated endotracheal intubation, with the Sellick maneuver applied to prevent aspiration. In all cases, we established controlled ventilation with a tidal volume of 8 ml/kg and a respiration rate of 12–14 breaths per minute. Anesthesia was maintained with a mixture of 1.5–2.0 vol% sevoflurane and 50% nitrous oxide in oxygen. If a maintenance dose was required, 0.15 mg/kg of rocuronium was added intravenously. Patients were extubated once they were fully awake to prevent aspiration.

Spinal anesthesia was introduced at L2/3 or L3/4 level with a 25-G pencil-point needle (Sprotte, Pajunk, Germany), with patients in a left lateral decubitus position; O₂ was supplied at a rate of 6 L/min via an oxygen mask. After confirming a clear, free flow of cerebrospinal fluid, 9–10 mg of 0.5% bupivacaine (Marcaine Heavy, Astra Zeneca, UK) with 10 μg fentanyl was injected slowly. Patients were then placed in a fully supine position and tilted 15° downward and leftward to prevent the supine hypotensive syndrome. The sensory block level was determined using a cold test. The operation was initiated when the sensory block had reached an adequate level (T4–T5). Phenylephrine (1 mg/h) was continuously infused to prevent arterial hypotension. If hypotension persisted, 0.1 mg phenylephrine was injected by IV bolus, or the continuous injection rate was increased up to 2 mg/h. If hypertension occurred, the continuous injection rate was decreased to 0.5 mg/h or discontinued. We defined hypotension as systolic blood pressure below 90 mmHg or below 70% of the baseline blood pressure. After the newborn had been delivered, mothers were sedated with intravenous midazolam as required if she wanted.

Cesarean section was performed via a standard lower segment transverse uterine incision with basic monitoring, including heart rate and blood pressure. After the baby had been delivered, carbetocin (Inj. Hanlim, Korea) was routinely administered to induce uterine contraction.

### Measurements

Data on gestational age, parity, height, body weight, pre and postoperative systolic blood pressure (mmHg), heart rates (beats/min), hct (%), duration of hospital stay (day), surgical time, anesthesia time, time between skin incision and delivery, estimated blood loss (EBL), and transfusions were collected from medical records. EBL was measured by a visual estimation and a gravimetric method that involves weighing of soiled sponges and measurement of fluid in suction canisters. Newborns were evaluated by a pediatrician in terms of their sex, weight, and 1- and 5-min Apgar scores. Pediatricians were randomly assigned for the cesarean delivery.

We defined our primary outcome as the mean difference between the pre- and postoperative hematocrit, and the secondary outcome as the 1- and 5-min Apgar scores.

### Statistical analysis

The sample size required to detect a statistically significant difference between the pre- and postoperative hematocrit was determined using R software (version 3.5.3, R Development Core Team, Austria). The differences between the pre- and postoperative hematocrit were measured in a preliminary study (n = 10 for each), and the average difference of hematocrit in the general anesthesia and spinal groups was 5.06 (SD, 3.31) and 2.13 (SD, 4.02), respectively. Sample size was calculated with an effect size of 0.796, power of 80%, and an α-value of 0.05; accordingly, 26 subjects were needed in each group.

All statistical analyses were performed using R software (version 3.5.3). The normality of the distribution of continuous variables was analyzed using the Shapiro–Wilk test. We used independent t-tests to analyze continuous, normally distributed variables and the Wilcoxon rank-sum test to analyze continuous, non-normally distributed variables. Categorical variables were compared using the χ² test or Fisher’s exact test. Descriptive statistics are presented as mean ± standard deviation, median (IQR, 3Q), or percentage. Perioperative change in hct (%) was compared between the two anesthesia groups using repeated-measures analysis of variance, followed by Student’s t-test. A P value of less than 0.05 was considered statistically significant.

### RESULTS

Between January 2016 and December 2018, a total of 331 women (singleton pregnancies) underwent elective cesarean section at our hospital. In total, 44 patients were excluded owing to failed spinal anesthesia, placenta previa,
or coagulopathy. Thus, eventually, 287 patients were stratified into either a general anesthesia (n = 141) or spinal anesthesia (n = 146) groups (Fig. 1).

Demographic data showed no significant differences between the general and spinal anesthesia groups for demographic characteristics, except surgical time (56.9 ± 13.1 vs. 53.2 ± 11.1 min, P = 0.011) (Table 1).

Maternal and fetal data were as follows: there was no significant difference in preoperative systolic blood pressure between the general and spinal anesthesia groups (136.1 ± 17.2 vs. 132.1 ± 17.4 mmHg, respectively). However, postoperative systolic blood pressure was significantly higher in the general anesthesia group than in the spinal anesthesia group (136.8 ± 16.7 vs. 119.3 ± 12.7, respectively, P < 0.001) (Table 2).

Preoperative heart rate was different between the general and spinal anesthesia groups (81.6 ± 12.6 vs. 85.6 ± 13.9 beats/ min, respectively, P = 0.011). The postoperative heart rate was significantly higher in the general anesthesia group than in the spinal anesthesia group (93.2 ± 16.8 vs. 71.0 ± 12.7, respectively, P < 0.001) (Table 2).

The mean postoperative hct level was significantly lower in the general anesthesia group than in the spinal anesthesia group (31.4 ± 3.9% vs. 34.2 ± 4.7%, respectively), although the general anesthesia group had a significantly larger proportion of newborns with 1-min Apgar scores < 7 was not significantly different between the two groups, although the general anesthesia group had a significantly larger proportion of newborns with 5-min Apgar scores < 7 than the spinal anesthesia group (6/141 [4.3%] vs. 0/146

Table 1. Demographic Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>General (n = 141)</th>
<th>Spinal (n = 146)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>34.1 ± 4.6</td>
<td>33.5 ± 4.0</td>
<td>0.214</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.0 ± 5.2</td>
<td>161.1 ± 5.8</td>
<td>0.258</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72.1 ± 14.9</td>
<td>70.8 ± 11.2</td>
<td>0.458</td>
</tr>
<tr>
<td>Gestation (wk)</td>
<td>37.0 ± 2.1</td>
<td>37.3 ± 1.9</td>
<td>0.298</td>
</tr>
<tr>
<td>Gravidity</td>
<td>2 (2.4)</td>
<td>2 (1.3)</td>
<td>0.301</td>
</tr>
<tr>
<td>Operation (min)</td>
<td>56.9 ± 13.1</td>
<td>53.2 ± 11.1</td>
<td>0.011*</td>
</tr>
<tr>
<td>Anesthesia (min)</td>
<td>75.0 ± 14.4</td>
<td>77.5 ± 12.1</td>
<td>0.114</td>
</tr>
<tr>
<td>Skin incision to delivery</td>
<td>5.9 ± 2.2</td>
<td>6.2 ± 2.3</td>
<td>0.305</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or median (1Q, 3Q). *P value < 0.05.

Table 2. Maternal and Fetal Parameters

<table>
<thead>
<tr>
<th>Measures</th>
<th>General (n = 141)</th>
<th>Spinal (n = 146)</th>
<th>Mean difference (95% confidence interval)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative SBP</td>
<td>136.1 ± 17.2</td>
<td>132.1 ± 17.4</td>
<td>4.0 (–0.2, 8.0)</td>
<td>0.051</td>
</tr>
<tr>
<td>Postoperative SBP</td>
<td>136.8 ± 16.7</td>
<td>119.3 ± 12.7</td>
<td>17.5 (14.1, 21.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Preoperative HR</td>
<td>81.6 ± 12.6</td>
<td>85.6 ± 13.9</td>
<td>-4.0 (–7.1, –0.96)</td>
<td>0.011*</td>
</tr>
<tr>
<td>Postoperative HR</td>
<td>93.2 ± 16.8</td>
<td>71.0 ± 12.7</td>
<td>22.2 (18.7, 25.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Preoperative hct (%)</td>
<td>36.2 ± 3.4</td>
<td>36.5 ± 3.1</td>
<td>-0.3 (–1.1, 0.4)</td>
<td>0.404</td>
</tr>
<tr>
<td>Postoperative hct (%)</td>
<td>31.4 ± 3.9</td>
<td>34.2 ± 4.7</td>
<td>-2.8 (–3.8, –1.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>dhct</td>
<td>4.8 ± 3.4</td>
<td>2.3 ± 3.9</td>
<td>2.4 (1.6, 3.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>EBL (ml)</td>
<td>856.7 ± 117.9</td>
<td>819.9 ± 81.9</td>
<td>36.9 (13.2, 60.6)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Transfusion rate (%)</td>
<td>3 (2.1)</td>
<td>2 (1.4)</td>
<td>7.6 (–3.4, 8.8)</td>
<td>0.969</td>
</tr>
<tr>
<td>Hospital stay duration (day)</td>
<td>5.0 ± 0.6</td>
<td>5.0 ± 0.7</td>
<td>-0.0 (–0.2, 0.1)</td>
<td>0.924</td>
</tr>
<tr>
<td>Fetal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal weight (g)</td>
<td>2,974.8 ± 594.8</td>
<td>2,977.4 ± 620.3</td>
<td>-2.7 (–144.0, 138.6)</td>
<td>0.970</td>
</tr>
<tr>
<td>Apgar score (1 min)</td>
<td>31 (22.0)</td>
<td>23 (15.8)</td>
<td>6.9 (–2.1, 15.9)</td>
<td>0.178</td>
</tr>
<tr>
<td>Apgar score (5 min)</td>
<td>6 (4.3)</td>
<td>0 (0)</td>
<td>4.3 (0.8, 9)</td>
<td>0.012*</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number (%). SBP: systolic blood pressure, HR: heart rate, preoperative: before surgery, postoperative: 1 day after surgery, hct: hematocrit, dhct: mean difference of hct (preoperative hct-postoperative hct), EBL: Estimated blood loss. *P value < 0.05, †P value < 0.01.
Postoperative hct levels were lower than the preoperative hematocrit levels in both groups, and the hct levels were lower on postoperative day (POD) 3 than on POD 1. The hct levels on POD 1 and POD 3 were significantly lower in the general anesthesia group than the spinal anesthesia group (Fig. 2).

**DISCUSSION**

Our results show that general anesthesia tends to cause more bleeding than spinal anesthesia, as the postoperative mean EBL volume and the mean difference between the pre- and postoperative hct level was larger with general anesthesia than with spinal anesthesia.

Although cesarean section is used to promote maternal health and fetal well-being, the maternal morbidity and mortality rates associated with this procedure remain high. The maternal morbidity rate associated with a cesarean section is approximately 35.7% [8]. Perioperative bleeding is the main cause of death related to cesarean section; the EBL volume that requires transfusion is about 1,000 ml [9]. Maternal bleeding related to cesarean section is more common with general than regional anesthesia [3,4]. Increased maternal postoperative bleeding under general anesthesia than with regional anesthesia may be due to the uterine-relaxing effects of inhalation anesthetics [10].

Saygi et al. [11] performed a prospective randomized study comparing maternal and fetal outcomes between general and spinal anesthesia groups undergoing cesarean section. The postoperative hct levels (29.9 ± 3.2% vs. 32.2 ± 4.1%, P = 0.004) were significantly lower in the general anesthesia group than in the spinal anesthesia group, similar to our results.

In this study, EBL was higher, and postoperative hematocrit levels were lower in the general anesthesia group than in the spinal anesthesia group. Moreover, the postoperative heart rate seemed to increase to compensate for hypovolemia or anemia in the general anesthesia group. Interestingly, the operation time was significantly longer in the general anesthesia group than the spinal anesthesia group, apparently due to an increased rate of operative manipulations to stop bleeding.

Guay [12] reported that regional anesthesia had a clear effect on surgical blood loss, but this did not usually reduce the number of transfused patients. Similarly, in this study, there was no significant difference in the number of transfused patients between the two groups.

In this study, postoperative hematocrit levels were significantly lower in the general anesthesia group than in the spinal anesthesia group, but they were significantly lower on POD 3 than on POD 1 (Fig. 2). Erythropoiesis was reportedly increased by day 7 after surgical blood loss, such that the postoperative hct deficit was corrected by day 28 [13].

The present study used the Apgar score as an indicator of fetal well-being. The Apgar score is a comprehensive measure of the clinical and cardiopulmonary functions of newborns. The proportion of newborns with 1-min Apgar scores < 7 was not significantly different between the two groups, while the proportion with 5-min Apgar scores < 7 was significantly larger in the general anesthesia group than the spinal anesthesia group (6/141 [4.3%] vs. 0/146 [0%], respectively, P = 0.012) (Table 2).

Recent studies [3,14] reported no significant difference in

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**Fig. 2.** Perioperative hematocrit (%). POD 0: preoperative, POD 1: postoperative 1 day, POD 3: postoperative 3 days. *P < 0.01.
the 1- or 5-min Apgar scores of newborn babies under general versus spinal anesthesia for cesarean section. However, Tonni et al. [15] reported that, although the mother’s oxygen partial pressure and saturation were higher with general anesthesia than with regional anesthesia, the partial pressure of oxygen and umbilical cord blood pH in the general anesthesia group were lower than in the spinal and epidural groups. They hypothesized that newborns delivered under general anesthesia experience transient respiratory depression because anesthetics given to the mother cross the placental barrier and enter fetal circulation.

In this study, the proportion with 5-min Apgar scores < 7 was significantly larger in the general anesthesia group than the spinal anesthesia group. We supposed that anesthetic agents crossing the placenta might influence the fetus to some degree, although the fetus well tolerated them. Regional anesthesia can minimize the exposure of newborns to anesthetics and improve placental perfusion and oxygenation of the fetus due to sympathetic blockade. Therefore, regional anesthesia is preferable to general anesthesia during the cesarean section for both maternal and fetal safety.

Usually, the administration of general anesthesia is inevitable in cases of maternal coagulopathy or fetal distress. Neonatal respiratory depression accompanied by low Apgar scores and umbilical arterial and venous pH changes associated with general anesthesia is often transient. However, careful and appropriately administered general anesthesia has no significant adverse effects on fetuses or neonates [16].

Although many reports have shown that regional and general anesthesia are almost identical in terms of neonatal well-being, regional anesthesia, especially spinal, is recommended for elective cesarean section to avoid neonatal depression, especially for preterm delivery.

This study had some limitations. First, it was retrospective study, and we could not control all confounding variables that may have affected the outcomes. Second, the P values of some major results (Apgar scores) are relatively large; the sample size is relatively small. Therefore, the significant results might be purely by chance (random error). The sample size was based on the number of participants required to detect a statistically significant difference in the hct level, but not the Apgar score between the groups. Since spinal anesthesia for cesarean section was only introduced in our hospital two years ago, the maximum possible sample size for the spinal anesthesia group was 146. According to the power calculation, 232 subjects were needed in each group to detect statistically significant differences in Apgar scores. Thus, our findings regarding the Apgar scores should be interpreted with caution, and future research should include adequate sample sizes.

During cesarean section, general anesthesia group is associated with more maternal blood loss and a larger proportion of newborns with 5-min Apgar scores < 7 than spinal anesthesia.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Anaphylaxis is defined as a serious, life-threatening, generalized or systemic hypersensitivity reaction with a rapid onset [1]. Although anaphylaxis during anesthesia induction occurs only in approximately 1 of 20,000 cases, it can be life-threatening. Neuromuscular blocking agents, particularly, rocuronium and succinylcholine, are the most common cause of anaphylaxis during anesthesia.

**Background:** Perioperative anaphylaxis is a life-threatening clinical condition characterized by severe respiratory and cardiovascular manifestations. Neuromuscular blocking agents are the most common cause of anaphylaxis during anesthesia.

**Case:** We report a case of rocuronium-induced anaphylaxis treated with sugammadex. A 75-year-old female was scheduled to undergo spinal surgery. She had no history of allergies. After the injection of rocuronium, she developed hypotension and tachycardia, and skin rashes and urticaria appeared. The patient received sugammadex to delay the operation, and her vital signs were stabilized. On the 76th postoperative day, we performed intradermal tests for rocuronium, propofol, and cefazolin. Diluted rocuronium alone induced 14 mm of flare and 8 mm of wheal within 5 min, both of which disappeared within 15 min after the intradermal injection.

**Conclusions:** Sugammadex is a useful rocuronium antagonist that can be used to treat rocuronium-induced anaphylaxis.

**Keywords:** Anaphylaxis; Anesthesia; Rocuronium; Sugammadex; Shock; Treatment.

---

**CASE REPORT**

A written informed consent form was obtained for publication of this report. A 75-year-old female (weight, 51 kg; height, 146 cm) was scheduled to undergo a decompressive lumbar laminectomy and interbody fusion (lumbar level, 3-4 and 4-5) under general anesthesia. She had well-controlled hypertension. Five years earlier, she underwent an uneventful procedure under general anesthesia...
(transobturator vaginal tape operation). She reported no known allergy to medication, food, or latex. Results of pre-operative laboratory examinations, chest radiography, electrocardiography, transsthoracic echocardiography, thallium scan, and pulmonary function tests were normal.

On arrival in the operating room, she had a noninvasive blood pressure of 102/63 mmHg, a heart rate of 98 beats/min, and an oxygen saturation (SpO₂) at room air of 100%. After starting pre-oxygenation anesthesia induction, the patient received propofol (100 mg) for anesthesia induction and rocuronium bromide (50 mg) to facilitate tracheal intubation. Anesthesia was maintained with 4–8 vol% desflurane and target-controlled infusion of remifentanil (2 mg; 2 ng/ml). Thereafter, endotracheal intubation was performed. A 16-gauge peripheral intravenous cannula and a 20-gauge arterial line were placed. The results of the first arterial blood gas analysis were within the normal range (pH, 7.43; pCO₂, 37; pO₂, 168). The patient was placed in the prone position after administration of prophylactic antibiotics (cefazoline, 2 g).

Five minutes after the position change, which was performed 10 min after induction, an arterial blood pressure of 68/43 mmHg and sinus tachycardia of 113 beats/min were noted. Even though the skin test for sensitivity to cefazoline was negative, the prophylactic antibiotics were discontinued immediately and ephedrine (10 mg), phenylephrine (200 mg), 1,100 ml of crystalloid, and 500 ml of colloid were administered. The follow-up arterial blood analysis results remained unchanged. Despite these interventions, the blood pressure decreased further to 35/25 mmHg and the heart rate was 130 beats/min. Subsequently, dexamethasone (5 mg) and pheniramine (4 mg) were administered. However, the patient’s skin symptoms continued to worsen and spread from her trunk to her head. We strongly suspected an anaphylactic reaction, and epinephrine infusion (0.1 μg/kg/min) was started after administration of an intravenous epinephrine bolus. Despite appropriate traditional management, the skin symptoms worsened, and the situation was still critical. The epinephrine infusion dose was increased every minute and bolus drugs were needed to restore the blood pressure. A decision was made to delay the surgery and sugammadex (200 mg; 4 mg/kg) was administered to reverse the neuromuscular blockade because her train-of-four ratio was 0.2 [7]. Shortly thereafter, the patient’s arterial blood pressure recovered to the pre-induction level. Hemodynamic data after sugammadex injection were as follows: heart rate, 102 beats/min; blood pressure, 95/48 mmHg; and oxygen saturation, 100%. The patient was sedated with a bolus of midazolam and transferred to the intensive care unit for further observation. She was extubated within 30 min of arrival in the intensive care unit, and no further vasopressor support was required (Fig. 1).

The patient was discharged without any complications. One month later, she visited the Department of Allergy Medicine for the identification of the agent that caused her intraoperative anaphylaxis. Intradermal skin tests were performed four weeks later with rocuronium and cefazoline. A marked positive, persistent, wheal-and-flair response was recorded at the site of rocuronium injection, comparable to that of the positive control (histamine), with negative responses at the other sites. Three months later, she decided to undergo surgery again. In the operating room, the patient received an induction dose of propofol and cisatracurium instead of rocuronium. Thereafter, endotracheal intubation was performed, and the surgery was conducted successfully in the prone position. No adverse events occurred intraoperatively, and the patient was discharged without any complications.

**DISCUSSION**

This case report describes the usefulness of intraoperative sugammadex administration in treating an episode of confirmed rocuronium-induced anaphylaxis, which was temporally associated with a marked improvement in the

![Fig. 1. Chart showing the vital sign changes. HR: heart rate, SBP: systolic arterial blood pressure, DBP: diastolic arterial blood pressure. *Rocuronium injection and intubation. †Epinephrine. ‡Sugammadex intravenous injection.](www.anesth-pain-med.org)
The reported incidence of anaphylaxis induced during anesthesia has varied from 1:3,500 to 1:20,000 [8,9]. Most cases have been reported in women and during the use of muscle relaxants. Neuromuscular blocking agents (NMBAs) account for most IgE-mediated anaphylactic reactions that occur during general anesthesia induction [8,10]. Among the muscle relaxants that induce anaphylaxis, rocuronium is the most common causative drug [11]. NMBAs induce the release of tryptase and histamine from mast cells, both of which have direct vasodilatory effects on the blood vessels and induce changes in capillary permeability, urticaria, erythema, angioedema, hypotension, and bronchospasm [12]. Independent risk factors associated with death were male sex, emergency setting, history of hypertension or other cardiovascular diseases, ongoing beta-blocker treatment, and obesity [13].

According to the World Allergy Organization (WAO), the diagnosis of anaphylaxis depends on the recognition of characteristic symptoms and signs that occur minutes to hours after exposure to a known or potential trigger [1]. Although the intradermal skin test or skin prick test are the gold-standard methods for identifying a potential anaphylactogen, they are indicators of the procedure and test concentrations used for most drugs. The optimal interval between the time of anaphylactic shock and the skin test is controversial. The test is commonly recommended in a minimum time interval of three weeks and no more than three months after the anaphylactic episode. In our case, intradermal skin test to identify the anaphylactogen was performed four weeks after the episode of anaphylactic shock.

When a patient is experiencing an anaphylactic shock, prompt acknowledgement as well as rapid and specific management is essential, including intravenous fluid replacement and the use of cardiovascular drugs. Epinephrine is the first-choice drug used to treat anaphylaxis [1]. Once an agent has been administered intravenously, it is difficult to eliminate it from the body. Sugammadex is a γ-cyclodextrin derivative with a truncated cone-like shape and a hydrophobic cavity. The molecular cavity of sugammadex encapsulates the steroid backbone of rocuronium with high affinity. Once enveloped within the sugammadex molecule, rocuronium cannot bind to acetylcholine receptors. This mechanism of sugammadex has a positive effect during the treatment of rocuronium-induced anaphylaxis [5].

Cases of sugammadex-induced anaphylaxis have been reported in countries that frequently use the drug. These cases of anaphylactic reactions appear to be more frequent at higher clinical doses [6]. Although sugammadex-induced anaphylaxis has been reported, sugammadex is a great antagonist of rocuronium. The optimal dose of sugammadex in such cases is unknown. Theoretically, it has been suggested that large doses (up to 16 mg/kg) may be required to encapsulate all circulating rocuronium molecules in a patient’s body [5]. This dose is dependent on the initial dose of rocuronium administered and the time elapsed since its administration. In our case, 200 mg of sugammadex was administered because it was readily available. In the present case, this dose appeared to fully reverse the underlying neuromuscular block, as expected given that 80 min had elapsed since rocuronium administration [14,15].

In conclusion, although cases of sugammadex-induced anaphylaxis have been reported, sugammadex is a useful rocuronium antagonist. It is noteworthy that sugammadex adequately reversed the adverse effects of rocuronium-induced anaphylaxis; however, the optimal dose to prevent anaphylaxis has not been reported yet. Therefore, further studies should be conducted to identify the optimal dose.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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REFERENCES


Comparison of postoperative pulmonary complications between sugammadex and neostigmine in lung cancer patients undergoing video-assisted thoracoscopic lobectomy: a prospective double-blinded randomized trial

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Background: Reversal of neuromuscular blockade (NMB) at the end of surgery is important for reducing postoperative residual NMB; this is associated with an increased risk of postoperative pulmonary complications (PPCs). Moreover, PPCs are associated with poor prognosis after video-assisted thoracoscopic surgery (VATS) for lobectomy. We compared the effects of two reversal agents, sugammadex and neostigmine, on the incidence of PPCs and duration of hospital stay in patients undergoing VATS lobectomy.

Methods: After VATS lobectomy was completed under neuromuscular monitoring, the sugammadex group (n = 46) received sugammadex 2 mg/kg, while the neostigmine group (n = 47) received neostigmine 0.05 mg/kg with atropine 0.02 mg/kg after at least the third twitch in response to the train of four stimulation. The primary outcome was incidence of PPCs. The secondary outcomes were duration of hospital (P = 0.431) and ICU (P = 0.964) stays.

Results: There was no significant difference in the incidence of PPCs for both the sugammadex and neostigmine groups (32.6% and 40.4%, respectively; risk difference = 0.08; 95% confidence interval = [−0.12, 0.27]; P = 0.434). The lengths of hospital (P = 0.431) and ICU (P = 0.964) stays were not significantly different between the two groups.

Conclusions: The clinical use of sugammadex and neostigmine in NMB reversal for patients undergoing VATS lobectomy was not significantly different in the incidence of PPCs and duration of hospital and ICU stay.

Keywords: Enhanced recovery after surgery; Neostigmine; Neuromuscular blockade; Postoperative complications; Sugammadex; Thoracic surgery, video-assisted.

INTRODUCTION

The primary goal of enhanced recovery after surgery (ERAS) in lung surgery is to optimize perioperative and intraoperative management to reduce postoperative complications and decrease the length of hospital stay [1,2]. Par-
MATERIALS AND METHODS

The study was approved by the Institutional Review Board (no. DAUHIRB-18-047) and was conducted between April 2018 and May 2020. Informed written consent was obtained from patients who were scheduled for elective surgery before enrollment and who voluntarily agreed to participate. One hundred and two patients were enrolled, who underwent VATS lobectomy, had an American Society of Anesthesiologists physical status of I–III, and were over 18 years old. Cases with open conversion during the operation were excluded. This randomized and double-blinded prospective study was registered at the Korea Clinical Research Information Service (no. KCT 0003891).

Using a computer-generated random number, 102 participants were randomly allocated to the neostigmine group (n = 51) or sugammadex group (n = 51) in parallel; this was performed by the main researcher (1:1 assignment ratio), who did not participate in anesthesia and was not involved in data collection. Ten milliliters of study drug solution was prepared in normal saline by the main researcher, based on the patient’s body weight. The sugammadex group was administered sugammadex 2 mg/kg, while the neostigmine group was administered neostigmine 0.05 mg/kg (maximum 5 mg) with atropine 0.02 mg/kg. The study drug was labeled as reverse after being shielded with a silver foil, and it was delivered to the anesthesia nurse.

All patients were administered 0.2 mg glycopyrrolate intramuscularly and 20 mg famotidine intravenously as premedication. Non-invasive blood pressure, electrocardiography, pulse oximetry, bispectral index (BIS) (Aspect Medical Systems, USA), and neuromuscular monitoring (TOFs can®, Dräger, France) were performed when the patients arrived at the operating room.

Anesthesia was induced by two blinded anesthesiologists, each of whom had experience with over 50 cases of one-lung ventilation, using propofol 2 mg/kg and rocuronium 0.6 mg/kg for NMB. We performed bag-mask ventilation with 100% oxygen. After confirming muscle relaxation (no reaction in response to the train of four [TOF] stimulation), we performed endotracheal intubation using a double lumen endobronchial tube (DLT) (Shiley™, Covidien, USA). An arterial catheter and a central venous catheter were inserted. Anesthesia was maintained with sevoflurane 1.5–2.5 vol% to maintain a BIS of 40–60; remifentanil infusions (0.05–2 μg/kg/min) were administered for pain con-
control. To maintain a deep block, vecuronium (0.01 mg/kg) was administered as required (first twitch of the TOF response) [12]. Oxygen concentration in an air/oxygen mixture was adjusted to 100% according to arterial blood gas analysis (ABGA) results. During severe hypoxemia, continuous positive airway pressure was applied to the non-dependent lung [13]. The end-tidal CO₂ concentration was maintained between 35 and 40 cmH₂O, and the following lung-protective ventilation strategies were implemented [2,13]: low tidal volume (4-6 ml/ kg), positive end-expiratory pressure, and lung recruitment. Flexible fiber-optic bronchoscopy (ED 3.1 mm, Olympus Optical, Japan) was used at least twice to confirm correct placement of the DLT immediately following intubation and repositioning.

The intra-cuff pressure was maintained between 10 and 20 cmH₂O using a cuff pressure manometer (Cuff Pressure Gauge, VBM Medizintechnik, Germany).

When one-lung ventilation was complete, administration of vecuronium was terminated, and a patient-controlled analgesia device (GemStar™ Infusion System, Hospira, Inc., USA) was connected to the intravenous line. It contained fentanyl 30 μg/kg andراموسترن 0.6 mg in normal saline with a total volume of 100 ml, and it was delivered at 1 ml/h as a background infusion with a 1 ml bolus dose (10 min lock-out time). To reduce opioid consumption, 0.5% ropivacaine was infused at 5 ml/h through a pain buster (Pain Relief System, Halyard Health, Inc., USA) intercostally before the end of surgery [2].

At the end of surgery, the labeled NMB reversing agent was administered at the reappearance of the third twitch in response to the TOF stimulation. Tracheal and oral secretions were gently suctioned once. After suction was applied, lung recruitment was performed. Neuromuscular monitoring continued until the end of anesthesia, and the DLT was removed when the recovering TOF ratios (TOFR) reached 0.9, which is considered adequate recovery from NMB [7].

Postoperative care included chest tube use, intensive care unit (ICU) stay, intubation, and ventilation; postoperative hospital stay was routinely implemented according to VATS lobectomy guidelines at the department of thoracic surgery. Intraoperative ABGA, operation time, and duration of anesthesia were recorded.

The primary outcome was the incidence of PPCs including prolonged air leak, pneumonia and atelectasis, desaturation, and reintubation as confirmed from progress and discharge records. Prolonged air leakage was defined as an air leak present on day 6 after surgery. Pneumonia and atelectasis were diagnosed based on radiologic findings of the postoperative chest radiograph. Desaturation was defined as saturation levels less than 95% after removing the oxygen mask. Reintubation was performed when respiratory failure occurred. Atrial fibrillation was diagnosed based on electrocardiography findings, when the patient complained of symptoms, such as dyspnea, palpitation, and fatigue. Pulmonary thromboembolism was diagnosed based on computed tomography and D-dimer test results. The secondary outcomes were the length of hospital stay and duration of ICU stay.

**Statistical analyses**

Based on the results of Cho et al. [3], in which the overall incidence of PPCs was 54.8% in the control group and 26.3% in the experimental group, 46 subjects were needed in each group to detect statistically significant differences (α = 0.05, power = 0.80). Thus, 51 patients per group were enrolled to compensate for potential dropouts (drop rate = 10%).

Data were presented as means ± SD, number of patients (%) or medians (1Q, 3Q). Categorical variables were analyzed using the chi-squared or Fisher’s exact test. Continuous variables were analyzed using Student’s t-test. All reported P values were two sided, and P values less than 0.05 were considered statistically significant. Data were analyzed using SPSS version 26 software (IBM Corp., USA).

**RESULTS**

Of the 102 patients, nine were excluded due to conversion to open surgery (four in the neostigmine group and five in the sugammadex group) (Fig. 1). Table 1 shows the patient characteristics of both groups. There were no significant differences between the two groups in factors that could affect postoperative complications, such as smoking history, body mass index, American Society of Anesthesiologists physical status classification, lobectomy site, or medical history. Predictive postoperative forced expiratory volume in 1 s was statistically significant (P = 0.016); however, there is no clinical significance to this, since the absolute values were not low in either group.

In addition, there was no significant difference in anesthesia management during surgery in terms of the operation time, anesthetic time, ABGA results, and total vecuro-
nium usage during surgery between the neostigmine and sugammadex groups (Table 2).

As shown in Table 3, the incidence of PPCs was not significantly different between the sugammadex and neostigmine groups (32.6% vs. 40.4%, respectively; risk difference = 0.08; 95% confidence interval = [-0.12, 0.27]; P = 0.434). There were no significant differences in terms of specific cardiopulmonary complications.

As shown in Table 4, there was no significant difference in the length of postoperative hospital stay (P = 0.431) or duration of ICU stay (P = 0.964) between the two groups.

**DISCUSSION**

Apart from PRNMB, anesthesiologists need to consider other factors affecting the incidence of postoperative complications. As a cholinesterase inhibitor, neostigmine is not a direct reversal, and it is associated with muscle weakness. Muscle weakness induced by neostigmine usually occurs due to administration of the drug at a higher dose after a nearly complete recovery of NMB. This is associated with respiratory impairment, including an increased risk of atelectasis, pulmonary edema, desaturation, and longer hospi-
Table 2. Perioperative Management

<table>
<thead>
<tr>
<th></th>
<th>Neostigmine (n = 47)</th>
<th>Sugammadex (n = 46)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoperative ABGA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH (mmHg)</td>
<td>7.4 ± 0.0</td>
<td>7.4 ± 0.0</td>
<td>0.269</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>91.6 ± 16.6</td>
<td>92.8 ± 18.7</td>
<td>0.742</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>39.1 ± 4.3</td>
<td>37.3 ± 3.6</td>
<td>0.028</td>
</tr>
<tr>
<td>O₂ saturation (%)</td>
<td>96.4 ± 3.0</td>
<td>96.5 ± 2.1</td>
<td>0.853</td>
</tr>
<tr>
<td><strong>One lung ABGA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH (mmHg)</td>
<td>7.4 ± 0.1</td>
<td>7.4 ± 0.1</td>
<td>0.078</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>114.6 ± 66.4</td>
<td>113.3 ± 61.8</td>
<td>0.805</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>38.9 ± 4.1</td>
<td>39.0 ± 5.5</td>
<td>0.900</td>
</tr>
<tr>
<td>O₂ saturation (%)</td>
<td>96.0 ± 3.9</td>
<td>96.0 ± 3.5</td>
<td>0.912</td>
</tr>
<tr>
<td><strong>Two lung ABGA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH (mmHg)</td>
<td>7.4 ± 0.0</td>
<td>7.4 ± 0.1</td>
<td>0.142</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>269.8 ± 118.4</td>
<td>257 ± 113.5</td>
<td>0.539</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>36.4 ± 4.4</td>
<td>36.2 ± 5.0</td>
<td>0.993</td>
</tr>
<tr>
<td>O₂ saturation (%)</td>
<td>99.7 ± 0.7</td>
<td>99.6 ± 0.8</td>
<td>0.686</td>
</tr>
<tr>
<td>Total vecuronium usage (mg/kg)</td>
<td>0.158 ± 0.063</td>
<td>0.156 ± 0.054</td>
<td>0.899</td>
</tr>
<tr>
<td>Anesthetic time (min)</td>
<td>320 (285, 350)</td>
<td>333 (295, 371)</td>
<td>0.102</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>245 (210, 275)</td>
<td>238 (210, 304)</td>
<td>0.361</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or median (1Q, 3Q). ABGA: arterial blood gas analysis.

Table 3. Postoperative Complications

<table>
<thead>
<tr>
<th></th>
<th>Neostigmine (n = 47)</th>
<th>Sugammadex (n = 46)</th>
<th>RD (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of PPCs</td>
<td>19 (40.4)</td>
<td>15 (32.6)</td>
<td>0.08 (−0.12, 0.27)</td>
<td>0.434</td>
</tr>
<tr>
<td>Prolonged air leakage</td>
<td>5 (10.6)</td>
<td>2 (4.3)</td>
<td>0.06 (−0.04, 0.17)</td>
<td>0.435</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (4.3)</td>
<td>1 (2.2)</td>
<td>0.02 (−0.06, 0.01)</td>
<td>1.000</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>14 (29.8)</td>
<td>8 (17.4)</td>
<td>0.12 (−0.05, 0.29)</td>
<td>0.160</td>
</tr>
<tr>
<td>Desaturation</td>
<td>5 (10.6)</td>
<td>6 (15.0)</td>
<td>−0.07 (−0.21, 0.07)</td>
<td>0.348</td>
</tr>
<tr>
<td>Reintubation</td>
<td>1 (2.1)</td>
<td>0 (0.0)</td>
<td>0.02 (−0.02, 0.00)</td>
<td>1.000</td>
</tr>
<tr>
<td>Number of complications per patient (1/2/3)</td>
<td>13/4/2</td>
<td>11/4/0</td>
<td></td>
<td>0.379</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3 (6.4)</td>
<td>1 (2.2)</td>
<td>0.04 (−0.04, 0.12)</td>
<td>0.617</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or number only. RD: risk difference, 95% CI: 95% confidence interval, PPCs: postoperative pulmonary complications, PTE: pulmonary thromboembolism.

Table 4. Postoperative Care

<table>
<thead>
<tr>
<th></th>
<th>Neostigmine (n = 47)</th>
<th>Sugammadex (n = 46)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of oxygen mask use (min)</td>
<td>210 (120, 370)</td>
<td>225 (120, 375)</td>
<td>0.913</td>
</tr>
<tr>
<td>Oxygen saturation 24 h after surgery (%)</td>
<td>99.2 ± 1.2</td>
<td>98.6 ± 1.9</td>
<td>0.062</td>
</tr>
<tr>
<td>Chest tube removal (d)</td>
<td>2.0 (2.0, 3.0)</td>
<td>2.0 (2.0, 3.0)</td>
<td>0.994</td>
</tr>
<tr>
<td>ICU LOS (d)</td>
<td>1.0 (1.0, 1.0)</td>
<td>1.0 (1.0, 1.3)</td>
<td>0.964</td>
</tr>
<tr>
<td>Postoperative hospital LOS (d)</td>
<td>7.0 (6.0, 10.0)</td>
<td>8.0 (7.0, 10.0)</td>
<td>0.431</td>
</tr>
</tbody>
</table>

Values are expressed as median (1Q, 3Q) or mean ± SD. ICU: intensive care unit, LOS: length of stay.

tal stay [7,14]. Moreover, Abad-Gurumeta et al. [8] reported in a review article that even when extubation was achieved under high doses of neostigmine (> 0.6 mg/kg), at TOFR greater than 0.9, neostigmine administration was associated with atelectasis, pulmonary edema, tracheal re-intubation, and prolonged hospital stay. In addition, Schepens et al. [15] obtained computed tomography scans during the spontaneous breathing cycle (TOFR > 0.9) after administering neostigmine (0.06 mg/kg), sugammadex (15 mg/kg), or saline at a TOFR of 0.5 in rats. They found that rats being administered neostigmine exhibited a smaller relative contribution of diaphragm movement to the total change in...
l lung volume compared with sugammadex or saline. This may be due to the effect of neostigmine on neuromuscular transmission because the residually occupied acetylcholine receptors may decrease the efficiency of neuromuscular coupling at the diaphragm. In our research, the dose of neostigmine was predetermined; a dose of 0.5 mg/kg above the light block (TOFR > 0.4) may cause muscle weakness in high-risk patients and may be associated with the occurrence of complications. Furthermore, the risk of cardiovascular complications is also relatively high with neostigmine because of hemodynamic changes caused by bradycardia and cardiac arrhythmias [7]. However, theoretically, sugammadex is a selective relaxant-binding agent and has a lower risk of cardiopulmonary complications than a combination of neostigmine and atropine [3,6,7,16]. Moreover, sugammadex possibly reduces the time required for complete recovery from NMB without increasing the incidence of hypersensitivity or anaphylactic reactions, even in deep blocks [16–18]. Furthermore, in a systematic review by Patton et al. [16], sugammadex was found to be more cost effective and potentially time-saving intraoperatively than neostigmine. Thus, we theorized that sugammadex was effective in reducing the incidence of PPCs compared with neostigmine, thereby helping to reduce the length of hospital stay.

Nevertheless, the primary outcome of this study showed no statistical significance regarding the effect of sugammadex and neostigmine in the reversal of moderate to light NMB after VATS lobectomy. In the present study, neuromuscular monitoring was performed until the end of anesthesia, as the drug dose was predetermined, owing to the double-blind method. Administration of the reversal agent was performed at the moderate to light block (over TOF count 3) and observed when TOFR reached 0.9, which is considered adequate recovery from NMB; this was followed by tracheal extubation because tracheal extubation at TOFR less than 0.9 was associated with more complications, including hypoxia, upper airway obstruction, oxygen desaturation, micro-aspiration, and reintubation, than extubation at TOFR greater than 0.9 [8]. This would have contributed to reducing the incidence of PRNMB after reversal in the neostigmine group, resulting in reduced incidence of PPCs. In addition, Togioka et al. [19] recently reported that among the 200 older adults undergoing prolonged surgery (high-risk subjects), there was no significant difference in the incidence of PPCs between the sugammadex and neostigmine groups (33% vs. 40%, respectively; odds ratio = 0.74; 95% confidence interval = [0.40, 1.37]; P = 0.30).

They found that the contribution of reversal agent to decreased incidence of PPCs can be masked in the high-risk population through the impact of the disease on the incidence of complications. In the present study, the average age of the patient group was 64 years, and the average operation time was more than 3 h. In addition, the incidence of PPCs in patients undergoing VATS lobectomy is as high as 10–40% [20]. For these reasons, it is thought that the contribution of sugammadex to the reduction of PPCs may have been obscured by the high incidence of complications. Therefore, sugammadex did not show a statistical difference in reducing the incidence of PPCs compared with neostigmine (32.6% vs. 40.4%, respectively; risk difference = 0.08; 95% confidence interval = [-0.12, 0.27]; P = 0.434).

The secondary outcomes of this study showed no significant differences between the two groups in terms of the length of hospital stay, ICU admission, and chest tube removal. This suggests that there was no significant difference between the effect of neostigmine and sugammadex on the incidence of critical complications affecting the length of hospital stay and ICU stay. In addition, the department of thoracic surgery at our hospital routinely performs early chest tube removal to reduce pain and encourage early ambulation in order to reduce hospital stay, unless serious complications occur according to the ERAS, which may have also affected our results [1,7].

There were a few limitations in our study. First, it was not possible to confirm whether PRNMB was actually reduced because neuromuscular monitoring was not performed in the ICU after extubation. In addition, PRNMB and muscle weakness were not evaluated; therefore, it was not possible to confirm their correlation with PPCs.

In conclusion, in clinical use, the use of sugammadex in reversing NMB at a minimum TOF count of 3 did not reduce the incidence of PPCs in patients undergoing VATS lung lobectomy compared with neostigmine under quantitative neuromuscular monitoring. In addition, there was no difference in the duration of hospital and ICU stay between both groups. Therefore, more quantitative and large-scale studies in patient groups or surgeries with high incidence of complications are needed to demonstrate the benefits of sugammadex as a NMB reversal agent in the correlation between preoperative risk factors and PPCs.
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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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REFERENCES


INTRODUCTION

Since establishment of the Korean Network for Organ Sharing (KONOS) in 2000, allocation of deceased donor livers had been performed according to patient status using Child-Turcotte-Pugh (CTP) score [1]. This system is based on that of the United Network for Organ Sharing (UNOS). Since 2002, UNOS has maintained an allocation policy that relies on Model for End-stage Liver Disease (MELD) score, and this practice has been adopted in many countries to distribute deceased donor livers [2,3]. After several years of research and simulation, the allocation policy based on MELD score was implemented in Korea in June 2016 [3].

Although debates remain on the association between MELD score and surgical outcomes, the MELD score-based allocation policy has led to a reduction in the number of new registrations on waiting lists, lower mortality,
shorter listing time, and an increase in the number of liver transplantation (LT) without altering the overall graft and patient survival rates after LT. As prioritization of recipients has switched from time on the waiting list to the principle of "sickest first," the medical severity of recipient status has increased [4,5]. Obviously, MELD score-based allocation brings sicker patients to the operating room, and anesthetic management of these patients might be more challenging. Therefore, it is necessary to review the effect of the allocation policy change on anesthetic management of transplant recipients.

The aim of the present study was to analyze and report changes in patient status and anesthetic management before and after implementation of the MELD scoring system at a single institution.

**MATERIALS AND METHODS**

After obtaining approval from the Institutional Review Board (no. 2020-04-155), we retrospectively investigated adult patients who underwent deceased donor liver transplantation (DDLT) from September 2014 to May 2017. Included patients were divided into two groups according to allocation policy. Multiple organ transplantation, pediatric patients, and re-transplant cases were excluded. Thirty-seven patients underwent transplantation before the new allocation policy was adopted (CTP group) while 42 patients had surgery after the new allocation policy was implemented (MELD group).

According to the overall surgical policy at our institution, anastomosis of the liver graft was performed using a piggy-back technique without a veno-venous bypass, and intraoperative continuous renal replacement therapy (CRRT) was not administered. A cell salvage device was used routinely during LT. Transfusion guidelines for the hospital were hemoglobin 8 g/dl for packed red blood cells (RBCs), hemoglobin 9 g/dl for cell salvage blood, prothrombin time (PT) expressed as an international normalized ratio (INR) 3 for fresh frozen plasma (FFP), platelet count 30 K/μl for platelet concentrate, and fibrinogen 80 mg/dl for cryoprecipitate.

Patient age, sex, MELD and CTP scores at the time of allocation, prevalence of hepatorenal syndrome (HRS), preoperative use of CRRT, and primary liver disease were investigated. For intraoperative parameters, incidence of potassium level > 4.5 mEq/L before reperfusion and base excess < -10 mEq/L during surgery, blood loss, transfusion amount, operation time, and maximal vasoactive-inotropic score (VIS<sub>max</sub>) were analyzed. Lengths of pre- and postoperative stays in intensive care units (ICU), postoperative mechanical ventilation, and total hospital stay, along with the one-year patient and graft survival rates were analyzed. And the same parameters were analyzed by subdividing each group into high (> 30) and low MELD scores (≤30).

The amount of intraoperative blood loss was calculated using the concept of red cell mass (RCM). Lost RCM (ml) = estimated blood volume (ml) × (preoperative hematocrit in % - postoperative hematocrit in %) + (transfused packed RBCs in units × 213 × 70%) + (transfused cell salvage blood in ml × 55%) [6]. The VIS<sub>max</sub> was calculated using the following equation:

\[
VIS_{\text{max}} = \text{dopamine dose} (\mu g/kg/min) + \text{dobutamine dose} (\mu g/kg/min) + 100 \times \text{epinephrine (\mu g/kg/min)} + 10 \times \text{milrinone dose} (\mu g/kg/min) + 10,000 \times \text{vasopressin dose} (U/kg/min) + 100 \times \text{norepinephrine dose} (\mu g/kg/min)
\]

Continuous variables showing normality were analyzed using Student t-test and are expressed as mean ± standard deviation. Continuous variables that did not show normality were analyzed using Mann-Whitney U test and are expressed as median (1Q, 3Q). Categorical variables were presented as number and frequency and were compared using chi-square test or Fisher’s exact test. For all analyses, a P value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics software, version 25.0 (IBM Co., Armonk, NY, USA).

**RESULTS**

Table 1 summarizes the demographic characteristics of the patients. Although there was no difference in CTP score between the two groups, the MELD score was significantly higher in the MELD group than in the CTP group (36.5 ± 4.6 vs. 26.5 ± 9.4, P < 0.001). The incidence of HRS also was higher in the MELD group than in the CTP group (26 vs. 7, P < 0.001).

Intraoperative profiles are summarized in Table 2. Although preoperative hemoglobin concentration was not different between the two groups, the amount of packed RBC transfusion was higher in the MELD group than in the CTP group (5.0 ± 3.6 units vs. 3.4 ± 2.2 units, P = 0.025). Only one case in the CTP group received transfusion-free transplantation. The amount of blood loss, operation time, and VIS<sub>max</sub> were not significantly different between the two groups.
Table 1. Demographic Characteristics of the Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>MELD group (n = 42)</th>
<th>CTP group (n = 37)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>50.8 ± 11.6</td>
<td>53.1 ± 1.3</td>
<td>0.377</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>30/12</td>
<td>22/15</td>
<td>0.177</td>
</tr>
<tr>
<td>MELD score</td>
<td>36.5 ± 4.6</td>
<td>26.5 ± 9.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CTP score</td>
<td>11.2 ± 1.8</td>
<td>10.7 ± 1.9</td>
<td>0.615</td>
</tr>
<tr>
<td>HRS</td>
<td>26</td>
<td>7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Preoperative CRRT</td>
<td>13</td>
<td>3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Primary liver disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV-related</td>
<td>18</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>HCV-related</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Alcohol-related</td>
<td>14</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Others*</td>
<td>6</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number. MELD: Model for End-stage Liver Disease, CTP: Child-Turcotte-Pugh, HRS: hepatorenal syndrome, CRRT: continuous renal replacement therapy, HBV: hepatitis B virus, HCV: hepatitis C virus, NBNC: non-B, non-C, HCC: hepatocellular carcinoma. *Others include NBNC liver cirrhosis or HCC or autoimmune, unknown etc.

Table 2. Intraoperative Profiles of the Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>MELD group (n = 42)</th>
<th>CTP group (n = 37)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lost RCM (ml)</td>
<td>1,573.9 ± 1,400.1</td>
<td>1,472.2 ± 879.8</td>
<td>0.708</td>
</tr>
<tr>
<td>Transfused blood products</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Packed RBC (units)</td>
<td>5.0 ± 3.6</td>
<td>3.4 ± 2.2</td>
<td>0.025</td>
</tr>
<tr>
<td>Fresh Frozen Plasma (units)</td>
<td>4 (2, 8)</td>
<td>4 (2, 6)</td>
<td>0.159</td>
</tr>
<tr>
<td>Platelet concentrate (units)</td>
<td>1 (0, 1)</td>
<td>1 (0.25, 1)</td>
<td>0.133</td>
</tr>
<tr>
<td>Cryoprecipitate (units)</td>
<td>6 (0, 6)</td>
<td>6 (0, 6)</td>
<td>0.990</td>
</tr>
<tr>
<td>Cell Saver (ml)</td>
<td>985.5 (686.5, 1,438.8)</td>
<td>1,179.5 (552.3, 2,102.3)</td>
<td>0.682</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>399.4 ± 92.5</td>
<td>388.9 ± 61.7</td>
<td>0.566</td>
</tr>
<tr>
<td>Vt&lt;sub&gt;max&lt;/sub&gt;</td>
<td>38.0 ± 14.1</td>
<td>33.5 ± 14.3</td>
<td>0.170</td>
</tr>
<tr>
<td>Potassium &gt; 4.5 mEq/L before reperfusion (%)</td>
<td>10 (23.8)</td>
<td>8 (21.6)</td>
<td>0.823</td>
</tr>
<tr>
<td>Base excess &lt; ~10 mEq/L during LT (%)</td>
<td>20 (47.6)</td>
<td>14 (37.8)</td>
<td>0.381</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD, median (1Q, 3Q), or number (%). MELD: Model for End-stage Liver Disease, CTP: Child-Turcotte-Pugh, RCM: red cell mass, RBC: red blood cell, VIS<sub>max</sub>: maximal vasoactive-inotropic score, LT: liver transplantation.

Table 3. Postoperative Profiles of the Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>MELD group (n = 42)</th>
<th>CTP group (n = 37)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative ICU stay (d)</td>
<td>0 (0, 2.3)</td>
<td>0 (0, 2.8)</td>
<td>0.769</td>
</tr>
<tr>
<td>Postop ICU stay (d)</td>
<td>6 (4, 7.5)</td>
<td>6 (5, 7)</td>
<td>0.729</td>
</tr>
<tr>
<td>Postop MV (h)</td>
<td>36.9 ± 37.1</td>
<td>29.7 ± 41.8</td>
<td>0.451</td>
</tr>
<tr>
<td>Total hospital stay (d)</td>
<td>25.5 (19, 42.8)</td>
<td>23 (17.3, 33.5)</td>
<td>0.834</td>
</tr>
<tr>
<td>Graft loss</td>
<td>6 (14.3)</td>
<td>5 (13.5)</td>
<td>0.841</td>
</tr>
<tr>
<td>Patient survival, 1 year (%)</td>
<td>75.0</td>
<td>73.7</td>
<td>0.810</td>
</tr>
</tbody>
</table>

Values are presented as median (1Q, 3Q), mean ± SD, or number (%). MELD: Model for End-stage Liver Disease, CTP: Child-Turcotte-Pugh, ICU: Intensive care unit, MV: mechanical ventilation.

Pre- and postoperative ICU stay, total hospital stay, and patient and graft survival rates are presented in Table 3; no variables showed significant difference between the two groups.

In subgroup analysis, MELD score was significantly higher in the MELD group with score both ≤ 30 (median value: 29 vs. 19.9 ± 5.7, P = 0.005) and > 31 (median value: 40 vs. 36 ± 2.3, P = 0.048). Patients with a MELD score less than 30 numbered 5 patients in the MELD group while 22 in the CTP group (Fig. 1). Length of postoperative ICU stay was significantly shorter in the MELD group with low MELD score compared to the CTP group with low MELD score (median: 4 days vs. 5.5 days, P = 0.023). All other variables showed no significant difference (Tables 4, 5).
DISCUSSION

The MELD score is calculated by three objective laboratory test results, while the CTP score includes subjective variables such as ascites and hepatic encephalopathy. As CTP score has limitations in reflecting medical severity of patient condition and the subjective judgment of medical staff may play a role, MELD score may be superior to CTP score [4]. Indeed, there was a significant difference in MELD score between the two groups in the present study, while CTP score showed little difference.

The numbers of patients with HRS and those undergoing CRRT preoperatively were significantly higher in the MELD group. Preoperative kidney dysfunction may complicate intraoperative management of these patients due to intravascular fluid accumulation and shifts in acid-base status and electrolytes [8]. Meanwhile, the incidence of intraoperative K⁺ > 4.5 mEq/L before reperfusion or severe metabolic acidosis (base excess < –10 mEq/L throughout LT) showed no significant difference between the two groups. This finding can be explained as follows. Unlike acute renal failure, pulmonary edema, metabolic acidosis, or hyperka-
leukemia is not common in HRS, except in cases of excessive fluid therapy [9,10]. Any CRRT performed immediately before LT would partially adjust the acid-base balance and electrolytes. Also, in line with another report from our institution, serum potassium level and metabolic acidosis can be well controlled medically in recipients managed with preoperative CRRT [11]. However, the presence of HRS prior to transplantation is a strong predictor of mortality after LT [12]. The prognosis for patients with cirrhosis and renal failure is poor, and HRS is associated with the worst prognosis [9]. Further study of the long-term outcomes after the allocation policy change is required.

Prioritizing the sickest patients raises concerns, such as increased risk of intraoperative bleeding and increased frequency of transfusion. However, except for packed RBC transfusion, this study found no significant difference in patients following the allocation policy change. This result is similar to those of another study in which MELD score did not predict blood loss or blood product requirement during LT [13]. In a study that evaluated the effect of the MELD score-based allocation system in LT, increased blood loss and transfusion rates were noted [14]. However, consistent with our results, Varotti et al. [15] suggested that MELD score is an independent variable associated with increased perioperative packed RBC transfusion. In a study by Frasco et al. [16], MELD score and preoperative fibrinogen concentration were independent predictors of transfusion exposure. They detected significant differences in severity of disease at the time of transplantation (as indicated by a higher MELD score), degree of impairment of coagulation function, and need for transfusion of RBCs and component therapy by comparing living donor LT and cadaveric donor LT [16]. This outcome may explain our findings of increased packed RBC transfusion in the MELD group. The causes of bleeding during LT can be multifactorial, and there is a limit to predicting the amount of bleeding or transfusion using only MELD score. Despite these limitations and the relatively small sample size of this study, a larger amount of packed RBC transfusion in the MELD group may be a notable finding.

Preoperative INR in the MELD group was significantly higher than that in the CTP group (3.45 ± 2.87 vs. 2.30 ± 0.83, P = 0.020). This result was not unexpected because MELD score is calculated based on total bilirubin, INR, and creatinine. However, surprisingly, there was no significant difference in FFP transfusion rate between the two groups, which may be partly explained by rebalanced hemostasis. Multiple studies have shown that patients with cirrhosis have deficiencies in both the pro-coagulant and anticoagulant pathways, leading to a “rebalanced” coagulation system [17–19]. The extent of coagulopathy as measured by PT or INR does not appear predictive of bleeding complications, and the observed derangements in hemostatic variables might not translate to a diffuse bleeding risk during LT [17,20]. However, prediction, prevention, and monitoring of bleeding in patients with liver disease are complicated as a result of their extensive baseline changes and a more precarious hemostatic system in these patients [17,18]. Although some studies have reported no differences in bleeding or blood transfusion rates before or after using this coagulation testing [21], application of a viscoelastic coagulation test for liver transplantation may be recom-

### Table 5. Perioperative Profiles of the Patients with High MELD Score (> 30)

<table>
<thead>
<tr>
<th>Variable</th>
<th>MELD group (n = 37)</th>
<th>CTP group (n = 15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELD score</td>
<td>40 (35, 40)</td>
<td>36 ± 2.3</td>
<td>0.048</td>
</tr>
<tr>
<td>Lost RCM (ml)</td>
<td>1,198.5 (907.5, 1,713.9)</td>
<td>1,730.9 (1,153.6, 2,482.6)</td>
<td>0.164</td>
</tr>
<tr>
<td>Transfused blood products</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Packed RBC (units)</td>
<td>4 (3, 6.5)</td>
<td>4.5 (2, 6)</td>
<td>0.848</td>
</tr>
<tr>
<td>Fresh frozen plasma (units)</td>
<td>4 (2, 8)</td>
<td>6 (4, 6.5)</td>
<td>0.699</td>
</tr>
<tr>
<td>Platelet concentrate (units)</td>
<td>1 (0, 1)</td>
<td>1 (1, 1)</td>
<td>0.060</td>
</tr>
<tr>
<td>Cryoprecipitate (units)</td>
<td>6 (0, 6)</td>
<td>6 (3, 6.3)</td>
<td>0.473</td>
</tr>
<tr>
<td>Cell saver (ml)</td>
<td>965 (686, 1,440)</td>
<td>1,478 (292.5, 3,723.8)</td>
<td>0.473</td>
</tr>
<tr>
<td>Vismax (mm)</td>
<td>37.3 ± 14.2</td>
<td>36.3 ± 13.6</td>
<td>0.825</td>
</tr>
<tr>
<td>Postop ICU stay (d)</td>
<td>6 (5, 9.5)</td>
<td>6 (5, 8.8)</td>
<td>0.543</td>
</tr>
<tr>
<td>Total hospital stay (d)</td>
<td>28 (19, 45)</td>
<td>26 (18, 32.5)</td>
<td>0.627</td>
</tr>
<tr>
<td>Graft loss</td>
<td>6 (16.2)</td>
<td>2 (13.3)</td>
<td>0.891</td>
</tr>
<tr>
<td>Patient survival, 1 year (%)</td>
<td>64.9</td>
<td>66.7</td>
<td>0.443</td>
</tr>
</tbody>
</table>

Values are presented as median (1Q, 3Q), mean ± SD, or number (%). MELD: Model for End-stage Liver Disease, CTP: Child-Turcotte-Pugh, RCM: red cell mass, RBC: red blood cell, VISmax: maximal vasoactive-inotrop score, ICU: intensive care unit.

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mended to reduce the incidence of bleeding and blood transfusion. This test has the advantage of reflecting the overall process of coagulation, and it is more sensitive and accurate at diagnosing coagulopathy than conventional coagulation test performed during the surgery [22].

The VIS is a scale showing the amounts of vasoactive and inotropic support [7]. We analyzed VIS_{max} to identify any change in vasopressor support during LT and found no statistically significant difference. However, Xia et al. [23] reported that patients with a high (> 30) MELD score required more vasopressors both before and during LT, although they only indicated whether a vasopressor was administered and did not specify the amount. VIS_{max} was higher in the high-MELD score patients in the CTP group than in the low-MELD score patients, although the difference was not statistically significant (31.7 ± 14.7 vs. 36.3 ± 13.6, P = 0.071). Only five patients in MELD group had a low MELD score, and the VIS_{max} analysis in the MELD group was limited. Further exploration with a larger sample size is necessary.

Giving priority to the sickest patient has the potential to create other concerns such as longer ICU stay. Oberkofler et al. [12] reported that MELD score greater than 23 was an independent risk factor for morbidity represented by ICU stay longer than 10 days. Oberkofler et al. [12] also found that transfusion of more than seven units of packed RBCs was an independent risk factor for mortality and prolonged ICU stay. Otherwise, there was no significant difference in duration of ICU stay in the present study. A similar group of patients reported by our institution showed no significant difference in six-month survival rate or in-hospital stay, but complication and readmission rates within the first three months were higher in the MELD group [24]. The one-year survival rate analyzed in this study did not differ significantly between the two groups. This finding is consistent with the results of other studies that overall patient survival after change to MELD scoring was not worse than that based on the pre-MELD criteria [9,25,26].

This study had certain limitations. It utilized a retrospective study design based on single-center data and a small sample size. Temporal changes in clinical practice would have influenced the results beyond a change in allocation system. In addition, demographics and underlying physical status of the donor and quality of the graft, which may influence the need for transfusions and vasopressors, were not addressed in the study. Also, the data included only DDLT, so the results may differ in LDLT recipients.

Contrary to our expectations, although the patient’s objective condition worsened, perioperative parameters did not change significantly. This outcome may be attributed to advances in perioperative monitoring skills, improved proficiency of surgeons, or more sophisticated ICU management. Our finding can also be explained by the shorter postoperative ICU stay of the MELD group than that of the CTP group in participants with low MELD score. Despite these limitations, this topic is important, especially from the anesthesiologist’s perspective. The parameters were compared immediately before and after conversion to the MELD score-based allocation system, and also were compared by dividing the patients into groups according to MELD score. In addition to the results shown by the parameters, it was clear that objective patient condition had deteriorated, and that it is difficult to predict the patient progress during LT. As a result, more detailed perioperative care is required in the MELD era.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conceptualization: Gaab Soo Kim. Data acquisition: Seung Yeon Yoo, Gaab Soo Kim. Data analysis: Seung Yeon Yoo. Writing-original draft: Seung Yeon Yoo. Writing-review & editing: Seung Yeon Yoo, Gaab Soo Kim.

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3. Kim MS. Modification of emergency status in deceased donor


Hereditary angioedema (HAE) is a rare, life-threatening autosomal dominant disorder caused by a deficiency of C1 esterase inhibitor (C1-INH), with an estimated prevalence of 1:50,000 [1,2]. HAE can be classified by the levels of C1-INH. Type I is diagnosed by low levels of C1-INH and C, and type II is diagnosed by normal levels but dysfunctional C1-INH [1,2]. HAE is potentially fatal because it may present with sudden life-threatening edema of the skin and aerodigestive tract (face, extremities, larynx, genitals, and trunk) recurrently or spontaneously [2,3]. Thus, patients are recommended to avoid general anesthesia with endotracheal intubation, or careful prophylactic therapies before surgery are required if surgery with general anesthesia is unavoidable. Besides the well-known clinical presentations, HAE may also produce hypovolemic shock due to the tissue leakage of fluids [4] and may lead to potentially
life-threatening conditions such as capillary leak syndrome (CLS) and disseminated intravascular coagulation (DIC) [5,6]. Here, we report a case of suspected CLS and DIC after kidney transplantation in a patient with HAE. The Institutional Review Board approved the study (CHOSUN 2020-05-005) to publish in a case report and granted a waiver of consent from the patient.

CASE REPORT

A 42-year-old male patient (height: 165 cm, weight: 61.7 kg) was admitted due to acute kidney injury with dyspnea. He complained of swelling in the face and upper arms, which occurred once or twice per year for 30 years. He could not remember his familial history. During admission, the patient’s facial swelling got worse and HAE was suspected. According to the laboratory results, the level of C4 and C1-INH were 7.15 mg/dl (normal range: 10–40 mg/dl) and 5.0 mg/dl (normal range: 21–39 mg/dl), respectively. The patient was treated with high doses of androgen therapy (Danazol, Young Poong Pharma, Korea; 600 mg daily) as prophylactic maintenance therapy for the swelling due to HAE. However, his kidney injury worsened and progressed to chronic kidney disease. A decision for kidney transplant surgery was made, and he received hemodialysis until surgery.

Seven months later, the patient was selected as the recipient of a kidney from a deceased donor and emergency surgery was planned. However, his level of C1-INH was still low (15.7 mg/dl), and there was a risk of edema developing during surgery. Thus, three units of fresh frozen plasma (FFP) were administered about one hour before surgery because C1-INH concentrate was not available due to the suspension of imports in Korea, although it was designated as an orphan drug. Anesthesia was induced with thiopental sodium (5 mg/kg) and cisatracurium (0.17 mg/kg). Careful intubation by video-laryngoscopy was performed with a 7.5 mm microcuffed endotracheal tube (Taper Guard®, Mallinckrodt, Ireland). The cuff pressure was adjusted to 20 cmH₂O using a cuff manometer (Mallinckrodt) and confirmed air leakage at an airway pressure of more than 20 cmH₂O. Anesthesia was maintained with desflurane and remifentanil, and mechanical ventilation was done with a fresh gas flow of 3 L/min of an oxygen/air mixture. His vital signs were maintained within 30% of the baseline during surgery. The surgery took about four hours. The administered fluid and estimated blood loss were 1,000 ml and 400 ml, respectively. At the end of the surgery, neuromuscular blockade was confirmed (train-of-four > 99%) after the administration of reversal agents (10 mg of pyridostigmine and 0.4 mg of glycopyrrolate). After confirming the absence of edema in the larynx by video-laryngoscopy, early extubation with mask ventilation before restoration of consciousness of the patient was done to avoid irritation of the larynx. The patient recovered consciousness and adequate respiration and was transferred to the aseptic intensive care unit (ICU). Immunosuppressants (tacrolimus and thymoglobulin), ganciclovir, and prostaglandin E1 were administered according to the hospital protocol. After surgery, his vital signs remained stable and urine output was about 190 ml after reperfusion during the hour in the ICU. During the night, his hemoglobin level remained at 9.4 g/dl and there were no abnormalities in the laboratory coagulation tests (platelet count, 202,000; prothrombin time [PT], 11.5 s; activated partial thromboplastin time [aPTT], 20.7 s; and international normalized ratio [INR], 1.04).

The next morning, the patient complained of dyspnea with abdominal discomfort. Then, hypotension (60/30 mmHg) and tachycardia (130 beats/min) developed, and he lost consciousness (Fig. 1). He was intubated and mechanical ventilation was applied, and norepinephrine and dobutamine were administered for the treatment of hypotension. At that time, abdominal distension with massive serosanguineous fluids (> 1,000 ml) in the drainage was found and generalized edema with low urine output (10 ml over eight hours) was also observed. He showed a low hemoglobin level (7.3 g/dl) with coagulopathy (PT, 22.8 s; aPTT, 44.1 s; and INR, 2.04), and DIC was diagnosed (fibrinogen < 100 mg/dl; fibrin degradation product, FDP 221 μg/ml; and D-dimer, 27,699 ng/ml). Thus, transfusion was performed (red blood cells six units; FFP, three units; cryoprecipitate 10 units: and apheresis platelets, one unit), and continuous renal replacement therapy (CRRT) was applied. Despite the treatments, there was no improvement in his conditions, and an emergency second-look operation was performed with the suspicion of leakage at the anastomosis site. However, there was no anastomosis leakage and normal blood flow to the kidney was confirmed by Doppler. Thus, the operation ended without specific treatment.

However, severe generalized edema with hypoaalbuminemia (2.5 g/dl) was sustained after surgery, although the C1-INH level had increased to 22.9 mg/dl after the contin-
Preparing emergency kidney transplantation
- Danazol 400 mg PO
- FFP 3U transfusion
Emergency Operation - DDKT

Diagnosed hereditary angioedema
- Danazol 400 mg oral medication

Generalized edema
Urine output (−)
Disseminated intravascular coagulation
Loss of consciousness

Hypotension (60/30 mmHg)
Tachycardia (130 beats/min)
Serosanguineous drainage (> 1,000 ml/day)
Pneumonia
Pulmonary edema
Rejection of transplanted kidney
Sustained severe hypotension
- No response to hemodynamic drugs

CRRT started
Intubation - Mechanical ventilation
Transfusion
Emergency second look operation
- No anastomosis leakage
- Normal blood flow to kidney (Doppler)

6 months before operation
Operation
POD #1
POD #2
POD #3
POD #4
POD #5

C1-INH (mg/dl)
5.0
15.7
10.6
10.5
9.4
7.8

Hb (g/dl)
12.9
7.3
10.6
10.5
9.4
7.8

WBC (x10^3/μl)
6.55
6.36
19.31
12.85
12.1
0.52

Albumin (g/dl)
4.26
2.5
2.82
2.79
2.43
2.31

BUN (mg/dl)
64.5
26.6
35.6
19.5
20.1
18.7

Creatinine (mg/dl)
14.42
7.76
9.64
3.41
3.2
2.01

Coagulation test
PT
11.5
22.8
25.3
25.4
29.3

INR
1.04
2.04
2.26
2.27
2.61

a-PTT
20.7
44.1
30.7
37.1
54.2

Fibrinogen (mg/dl)
< 100
169
131
126
123

FDP (μl/ml)
221
216
230
105
33.5

D-dimer (ng/ml)
27,699
26,626
12,983
3,855

Input
Crystalloid (ml)
2,000
3,130
10,820
8,980
13,230

FFP (unit)
4
3
2
2

RBC (unit)
6
4
2
2

20% Albumin
2
2
2
2

Output
Urine output (ml)
1,049
3,017
5,815
6,364
4,725

Drainage (ml)
190
10
30
30
15

CRRT (ml)
2,007
4,480
4,828
3,316

uous administration of 20% albumin, danazol at 400 mg via a Levin tube, and FFP transfusions. We thought that the worsening of the patient’s condition despite increases in the C1-INH level was due to harmful substrate proteins in the FFP, and would be transient. The laboratory blood culture results showed no evidence of bacterial growth. Despite intensive care with hypotensive drugs, transfusions, and CRRT, his condition worsened because of sustained generalized edema with hypoalbuminemia, coagulopathy, and DIC. On the fourth day after the surgery, pulmonary edema, pneumonia, and rejection of the transplanted kidney developed and sustained severe hypotension without response to hemodynamic drugs was seen. The patient’s guardians did not want any additional treatment and the patient died because of shock after a day.

**DISCUSSION**

The complement system contributes to the immunological defense mechanism of the body. HAE is caused by a SERPING1 gene (Serine Protease Inhibitor Gene 1 present on the Long Arm of Chromosome 11 [11q]) defect, which results in decreased or dysfunctional C1-INH [1–3]. Although HAE attacks are unpredictable and the triggering factors are unclear, numerous physical stimuli such as dental and surgical procedures, emotional stress, infections, and medications can be triggering factors of life-threatening angioedema [1–3]. Still, there are no definite perioperative guidelines for the prophylaxis of an HAE attack. However, the following prophylactic therapy is usually suggested: C1-INH concentrate, 1,000 units before surgery; androgens such as danazol (400 to 600 mg/day), five days before and five days after surgery or a procedure; and FFP (two units for adults, 10 ml/kg in children), one to two hours before surgery [1–3]. Among those treatments, C1-INH concentrate or androgens is known to have the best effect. Tranexamic acid can also be used for long-term prophylaxis, especially in children, but it has not been recommended recently because it has little benefit as short-term prophylaxis or for the acute treatment of HAE attacks due to its delayed onset of action [7]. However, some patients undergo HAE attacks after surgical procedures despite prophylaxis. Thus, careful approaches to the patient with rescue management are required [3].

The patient in our case was diagnosed with type I HAE with low levels of C1-INH and C4, and we used the prophylactic administration of FFP instead of C1-INH concentrate before surgery because it was not available in Korea. Despite prophylactic treatment with FFP, generalized edema developed in the patient, and the catastrophic outcome of DIC developed. We will discuss the possible causes of the deterioration of the patient’s condition.

C1-INH plays an important role in the regulation of not only the classical pathway of the immune system but also the plasminogen- plasmin and kallikrein-kinin systems (contact system), and coagulation/fibrinolysis [8]. The deficiency or dysfunction of C1-INH in patients with HAE predominantly results in the increased activation of bradykinin by kallikrein, which leads to vasodilation, an increase in vascular permeability, and the typical angioedema of HAE. In patients with HAE, C3 and C1/C1-inhibitor complexes are easily activated by physical stress [9]. Especially, complement activation is associated with ischemia/reperfusion injury during cold storage of the organ and rejection, and is considered the major factor in graft failure after transplantation by triggering tissue damage and interfering with the anticoagulant and fibrinolytic capacity of the vascular endothelium [10]. Our patient was a kidney transplant recipient with the possibility of increased activation of the immune system. Therefore, it is thought that the regulation of complement activation would not be achieved after major surgery because of C1-INH deficiency in our patient, resulting in the acute rejection of the transplanted kidney by excessive complement activation.

CLS is one of the common complications associated with low C1-INH activity [10]. CLS is characterized by hypotension or multi-organ failure by massive third-space loss of fluids due to increased capillary permeability, which is accompanied by extravasation and diffuse edema. We considered CLS as the cause of the sustained hypotension because of the distinguishing features such as generalized edema with hypoalbuminemia despite albumin treatment, massive drainage of serosanguineous fluids from the intraabdominal space without anastomosis leakage, and the absence of anaphylaxis or sepsis, which should be ruled out due to similar characteristics [11]. Treatment for the prevention of antibody-mediated rejection after kidney transplantation has the potential risk for developing CLS [3].

C1-INH also plays a significant role in both coagulation and fibrinolysis [8]. The activation of C1-INH leads to thrombin generation and plasmin inhibition, which accounts for about 15% of the fibrinolysis. Hence C1-INH deficiency can lead to pathologic thrombosis. Generally, HAE
is not associated with coagulation properties clinically. However, there is a possibility that C1-INH deficiency might affect the coagulation system in the pathologic condition. Kodama et al. [12] revealed that the symptom of an HAE attack in older adults was hypercoagulation because activation of the complement system mainly activates the tissue factor pathway instead of the kallikrein-kinin system. Such physiologic changes with aging lead to the generation of thrombin and the activation of antithrombin-III during an HAE attack, which precipitates DIC. The hypercoagulability of pregnancy and intravascular fluid depletion due to increased vascular permeability during an HAE attack may also contribute to the development of DIC [6]. In our patient, DIC developed simultaneously from the severe intravascular volume depletion in the HAE attack. The decreased hemoglobin level due to DIC was misinterpreted as anastomosis leakage and interfered with the diagnosis of CLS.

In the treatment of acute HAE attacks, C1-INH concentrate, ecallantide (a kallikrein inhibitor) and icatibant (a bradykinin B2-receptor antagonist) are recommended as the first-line drugs [7]. However, as mentioned above, none of those drugs were available in Korea at that time, and it was very regrettable that they could not be administered to the patient. The administration of C1-INH concentrate restores the inhibitory action of complement system by correcting the C1-INH deficiency or dysfunction. Also, C1-INH concentrate is generally well-tolerated in the treatment of CLS after kidney transplantation caused by the preventive treatment of antibody-mediated rejection [11]. Daily intravenous infusions of C1-INH concentrate also showed effectiveness in patients with HAE accompanied by ascites, hypovolemic shock, and renal and respiratory failure who did not tolerate conventional ICU treatment [5]. Moreover, C1-INH concentrate is considered a multifunctional regulator of the cascade systems, which were recently shown to improve graft function by inhibiting complement activation and reducing the postoperative inflammation [10]. Our patient would have been better if he was treated with C1-INH concentrate. Fortunately, icatibant has recently become available in Korea and is thought to help severe HAE attacks like that of our patient because it can mediate vasodilatation and increase capillary permeability by preventing the receptor binding of bradykinin [7]. The use of FFP should only be considered when the first-line drugs are not available in an HAE attack. FFP is known as an effective substitute for C1-INH concentrate during HAE because it contains C1-INH. However, FFP may worsen the symptoms paradoxically because it contains not only C1-INH but also other substrates such as kininogens [3]. Therefore, the anesthesiologist should monitor the patient’s condition during an HAE attack treated with FFP. There is a possibility that the poor outcome of our patient despite the increase in C1-INH levels after the massive transfusion of FFP was due to the increase in harmful substrates administered in the FFP. Unfortunately, our patient had no option for treatment except FFP.

In conclusion, HAE is a disease with a decrease or dysfunction of C1-INH, which may lead to life-threatening complications such as CLS and DIC. Careful prophylactic therapy with androgen, FFP, and C1-INH concentrates is essential before surgery. However, in stressful conditions such as organ transplantation, HAE attacks may occur despite prophylactic treatment and produce fatal complications such as hypovolemic shock due to CLS and DIC. C1-INH concentrate may be an important option for severe HAE attacks. We experienced a case of suspected CLS and DIC after kidney transplantation in a patient with HAE. Unfortunately, we could not use C1-INH concentrate for the patient at the appropriate time. In Korea, C1-INH concentrate is not available. However, the use of recently proved icatibant might help treat a severe HAE attack. If those first-line drugs are not available, FFP should be used with careful monitoring. The anesthesiologist should understand the critical complications of HAE and prepare the appropriate treatment options.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conceptualization: Ki Tae Jung. Data acquisition: Jeong Wook Park, Jinyoung Seo. Supervision: Ki Tae Jung. Writing—original draft: Jeong Wook Park, Jinyoung Seo, Ki Tae Jung. Writing—review & editing: Sang Hun Kim, Ki Tae Jung.

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REFERENCES

INTRODUCTION

Chronic musculoskeletal pain is defined as pain that lasts for three to six months or beyond the time of normal healing [1]. Musculoskeletal disorders are the most common source of chronic musculoskeletal pain, and their increasing prevalence has led to a need for effective non-surgical solutions, such as physical therapy, pharmacologic treatment, and injection-based treatment [2]. Injection therapies can be introduced when pain or functional limitations are significant despite oral medication or exercise [3]. Corticosteroid injections are the most common regi-
men for musculoskeletal disorders; they provide short-
term symptomatic improvement, but aggravate cartilage
damage, thus increasing the risk of tissue atrophy [4].
Therefore, physicians have become interested in alterna-
tive injectants, such as prolotherapy or platelet-rich plasma
(PRP) [5].

Prolotherapy is a nonsurgical regenerative injection
technique that administers small amounts of an irritant
solution to the degenerated tendon insertions (entheses),
joints, ligaments, and adjacent joint spaces over a series of
several treatment sessions [6–8]. The mechanism of action
behind prolotherapy is not completely understood, but the
current theory is that the injected proliferate causes a heal-
ning process that is similar to the body’s natural healing pro-
cess, whereby a local inflammatory cascade is initiated,
which triggers the release of growth factors and collagen
deposition [2]. To date, many studies which support the
benefits of the use of prolotherapy in patients with chronic
musculoskeletal pain have been reported [9,10]. However,
few meta-analyses have analyzed the effect of prolotherapy
in patients with chronic musculoskeletal pain. Therefore,
we designed a meta-analysis to evaluate the effect of pro-
lotherapy in the treatment of chronic musculoskeletal pain
and compare the effect of prolotherapy with other treat-
ments.

MATERIALS AND METHODS

Study design

This meta-analysis was performed according to the rec-
nommendations of the PRISMA and Cochrane Collabora-
tion. The protocol was registered with PROSPERO (no.
CRD42019130609).

Information sources and search strategy

Two reviewers (WL, YL) systematically searched elec-
tronic databases such as Medline, Embase, and the Co-
chrane Library (CENTRAL) with no limitations on the year
of publication. Additionally, KoreaMed (https://koreamed.
org) and KMbase (http://kmbase.medric.or.kr) were used
to search for manually relevant domestic articles. Broad
search terms such as “prolotherapy”, “chronic osteoarthri-
tis”, and “randomized controlled trials”, were included
to achieve higher sensitivity, and Medical Subject Heading
(MeSH) terms were used. The languages of the articles
were limited to Korean and English. The last search was
conducted on March 10, 2019.

We did not search grey literature, despite its important
contribution to a systematic review, because we wanted to
present an effective basis for treatment to clinicians with as
little bias as possible, based on the results of RCTs.

Study selection and eligibility criteria

All relevant studies were independently screened by two
reviewers (WL and YL). Selection of relevant articles was
done primarily at the title and abstract level, then after at
the full-text level. Studies for the final assessment were se-
lected based on the agreement of the two reviewers. Any
disagreement was resolved by discussion with a third re-
viewer (SL).

Studies were included in the meta-analysis if they satis-
fied the following criteria: (1) patients with chronic muscu-
loskeletal pain lasting for more than 3 months; (2) pro-
lotherapy using dextrose for any joints, tendon, and/or lig-
aments; (3) results of the non-prolotherapy group were re-
ported; and (4) the post-injection pain score was reported
as the primary outcome.

Studies were excluded for the following reasons: (1) use
of prolotherapy solutions containing anything other than
sodium (polidocanol, manganese, zinc, human growth
hormone, phenol-glucose-glycerine, pumice, ozone, gly-
cerin, phenol, PRP, bone marrow, lipoadipase, stem cells, or
sodium morrhuate); (2) injection into the epidural space;
(3) did not report appropriate outcomes or outcome mea-
surements as mentioned; (4) non-randomized controlled
trials; (5) non-human studies; (6) articles not in English or
Korean.

Risk of bias in individual studies

Two independent authors (WL and YL) reviewed the ar-
ticles to assess the risk of bias (ROB) using the ROB tool
provided in the Review Manager software version 5.3 (The
Cochrane Collaboration, UK) based on Cochrane’s assess-
ment of the risk of bias [11]. If necessary, a third reviewer
(SL) was included in the discussion to sort out the dis-
agreements. The following eight domains were used to as-
sess the risk of bias in each trial: random sequence gener-
ation (selection bias), allocation concealment (selection
bias), blinding of participants and personnel (performance
bias), blinding of outcome assessment (detection bias), in-
complete outcome data (attrition bias), selective reporting (reporting bias), and other bias. The methodology for each trial was graded as “high”, “low”, or “unclear” to reflect a high risk of bias, low risk of bias, or uncertainty of bias, respectively. The agreement between the two independent reviewers for the level of risk of bias regarding the eight domains was assessed using Cohen’s kappa. Kappa values were interpreted as follows: 1) less than 0: less than chance agreement, 2) 0.01 to 0.20: slight agreement, 3) 0.21 to 0.40: fair agreement, 4) 0.41 to 0.60: moderate agreement, 5) 0.61 to 0.80: substantial agreement, and 6) 0.8 to 0.99: almost perfect agreement.

Data collection process and extracted items

Two authors (WL and YL) extracted data from the original articles, and another author (SL) independently confirmed all of the extracted data. The general characteristics (i.e., the study design, publication year, and name of the first author), intervention types and methods, and outcomes were extracted for each study based on the inclusion criteria. Each method of the intervention, such as the prolotherapy regimen, interval, and duration, was extracted. The measured outcomes included the number of patients analyzed in each group, tools for pain assessment, and pain scores.

The main outcome was determined by the severity of the pain, derived from the results of the pain scale. The first priority of pain measurement extraction was the pain score for 6 months to 1 year. To assess the effectiveness of dextrose prolotherapy, we used the standardized mean difference of pain scores between the prolotherapy group and other comparator groups using exercise, saline, PRP, and steroid injection.

Subgroup analysis

We grouped the analyses of VAS for pain into less than three months, three to six months, and more than six months while registering our review in PROSPERO. However, we were unable to classify the subgroups as originally planned because not all the individual studies followed the patients and reported the resulting variables on these criteria. Using the common denominator of the results of the individual studies, we were able to synthesize results that could be divided into three subgroups: baseline to 1 month, 1 month to 3 months, and 6 months to 1 year.

Statistical analysis

Continuous data (e.g., post-injection pain scores) were pooled as standardized mean differences (SMDs) because different outcome measurement scaling was expected across trials. We also calculated the 95% confidence intervals (CIs) for all estimates. A random-effect model was used to pool the study results, taking into account possible variations in effect sizes across trials. The heterogeneity statistic Cochrane Q and its corresponding degrees of freedom (df) and P value, as well as Higgins’ I2 as a measure of heterogeneity were calculated. P values < 0.05 were considered to be representative of statistically significant heterogeneity, and I2 values > 50% were considered to represent significant heterogeneity. Post-hoc subgroup analyses were performed where possible for each outcome to explore heterogeneity based on the different sites of injection. Chi-squared tests for heterogeneity were performed to identify differences between subgroups. Publication bias was not evaluated because only a few (< 10) studies were included in this meta-analysis. We conducted a sensitivity analysis to evaluate the influence of each study on the long-term (six months to one year) therapeutic effect of prolotherapy compared with saline by excluding one trial at a time from the pooled effects. All analyses were performed using R 3.5.1 (R Foundation for Statistical Computing, Austria) and Review Manager (RevMan, version 5.3, The Cochrane Collaboration).

RESULTS

Study selection and characteristics

We retrieved 680 articles after the initial database search: Medline (n = 250), EMBASE (n = 64), CENTRAL (n = 168), and Korean databases (n = 198).

After excluding 567 duplicate articles, primary selection was performed on 131 articles. First, we excluded 66 unrelated articles based on titles and abstracts. Second, we excluded 27 articles that only included abstracts. Thereafter, full-text reviews were conducted for 38 articles. Of these 38 full-text articles, 28 were excluded for the following reasons: not controlled with placebo or other treatment (n = 14), patients’ pain period not clearly described or less than three months (n = 9), duplication (n = 4), and articles not in English or Korean (n = 1). The reasons for exclusion of these papers are given in detail in Table 1. Finally, ROB
<table>
<thead>
<tr>
<th>Title</th>
<th>Author</th>
<th>Reason for exclusion</th>
<th>Journal/Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertonic dextrose injection (prolotherapy) for knee osteoarthritis: long term outcomes (2015)</td>
<td>Rabago D</td>
<td>Not RCT</td>
<td>Complementary Therapies in Medicine</td>
</tr>
<tr>
<td>The efficacy of prolotherapy for lateral epicondylitis: a pilot study (2008)</td>
<td>Scarpone M</td>
<td>Use of prolotherapy solutions containing anything other than glucose</td>
<td>Clinical Journal of Sport Medicine</td>
</tr>
<tr>
<td>The effects of injecting intra-articular platelet-rich plasma or prolotherapy on pain score and function in knee osteoarthritis (2018)</td>
<td>Rahimzadeh P</td>
<td>Uncertain pain period</td>
<td>Clinical Interventions in Aging</td>
</tr>
<tr>
<td>Qualitative assessment of patients receiving prolotherapy for knee osteoarthritis in a multimethod study (2016)</td>
<td>Rabago D</td>
<td>No controlled group</td>
<td>Journal of Alternative and Complementary Medicine (New York, NY)</td>
</tr>
<tr>
<td>Prolotherapy versus corticosteroid injections and phonophoresis for the treatment of plantar fasciitis: a randomized controlled trial (2015)</td>
<td>Demir G</td>
<td>Uncertain pain period</td>
<td>Arthritis and Rheumatology</td>
</tr>
<tr>
<td>Prolotherapy versus corticosteroid injections for the treatment of lateral epicondylitis: a randomized controlled trial (2011)</td>
<td>Carayannopoulos A</td>
<td>Use of prolotherapy solutions containing anything other than glucose</td>
<td>PM &amp; R: the Journal of Injury, Function, and Rehabilitation</td>
</tr>
<tr>
<td>Intra-articular hyaluronic acid injections vs. dextrose prolotherapy in the treatment of osteoarthritic knee pain (2012)</td>
<td>Hashemi SM</td>
<td>Turkish text</td>
<td>Tehran University Medical Journal</td>
</tr>
<tr>
<td>The effects of prolotherapy with hypertonic dextrose versus prolozone (intra-articular ozone) in patients with knee osteoarthritis (2015)</td>
<td>Hashemi M</td>
<td>Use of prolotherapy solutions containing anything other than glucose</td>
<td>Anesthesiology and Pain Medicine</td>
</tr>
<tr>
<td>Dextrose prolotherapy for knee osteoarthritis: results of a randomized controlled trial (2011)</td>
<td>Rabago DP</td>
<td>Duplicated study</td>
<td>Osteoarthritis and Cartilage</td>
</tr>
<tr>
<td>Benefit of dextrose prolotherapy in painful rotator cuff tendinopathy cases receiving physical therapy: a randomized controlled trial (2015)</td>
<td>Bertrand H</td>
<td>Duplicated study</td>
<td>Pain Research and Management</td>
</tr>
</tbody>
</table>

(Continued to the next page)
Title | Author | Reason for exclusion | Journal/Source
--- | --- | --- | ---
Association between disease-specific quality of life and magnetic resonance imaging outcomes in a clinical trial of prolotherapy for knee osteoarthritis (2013) | Rabago D | Use of prolotherapy solutions containing anything other than glucose | Archives of Physical Medicine and Rehabilitation
Hypertonic dextrose and morrhuate sodium injections (prolotherapy) for lateral epicondylitis (tennis elbow): results of a single-blind, pilot-level, randomized controlled trial (2013) | Rabago D | Use of prolotherapy solutions containing anything other than glucose | American Journal of Physical Medicine & Rehabilitation
Investigation the efficacy of intra-articular prolotherapy with erythropoietin and dextrose and intra-articular pulsed radiofrequency on pain level reduction and range of motion improvement in primary osteoarthritis of knee (2014) | Rahimzadeh P | Uncertain pain period | Journal of Research in Medical Sciences
Short term analgesic effects of 5% dextrose epidural injections for chronic low back pain: a randomized controlled trial (2017) | Maniquis-Smigel L | Epidural injection | Anesthesiology and Pain Medicine

Quality assessment of the included studies (risk of bias within studies)

ROB evaluation revealed an overall low risk for selection bias, performance bias, detection bias, attrition bias, and reporting bias, while almost half of the studies showed a high risk of performance bias because they could not blind the participants and five studies showed a high risk of detection bias. The risk of incomplete outcome data was high in four studies that did not mention a minimal sample size, resulting in an unclear risk of bias [14,17,19]. Four other studies did not meet minimal sample size criteria: two studies had high detection bias [15,17] because the injection site was different or because exercise was included in a control group. Two studies reported detailed information regarding the randomization techniques that we used, such as manual random number selection or a computer-generated random number table. Allocation concealment was unclear in five studies.

RCT: Randomized Controlled Trial.

All studies were randomized controlled trials. Various injection sites, including large joints such as the knee and small joints such as finger joints, were investigated. The comparator groups included saline injection, exercise, steroid injection, PRP injection, and extracorporeal shock wave therapy. The severity of pain was measured using the Visual Analog Scale (VAS), the Western Ontario and McMaster Universities Osteoarthritis Index, the Kannofsky Performance Score, and Foot Function Index. The concentration, volume of dextrose solution, and interval between injection sessions were different between studies. The dextrose concentration ranged from 5% to 25%, and the injection interval ranged from weeks to months.
Records identified through database searching
Medline (n = 250)
EMBASE (n = 64)
CENTRAL (n = 168)

Additional records identified through other sources
Korea DB (n = 198)

Records after duplicates removed (n = 567)

Records screened (n = 131)

Records excluded (n = 66)

Records 2nd screened (n = 65)

Abstract only (n = 27)

Full-text articles assessed for eligibility (n = 38)

Full-text articles excluded, with reasons (n = 28)
- Not controlled with placebo or other treatment (n = 14)
- Insufficient or not described pain period (n = 9)
- Not in Korean or English (n = 1)
- Duplicated study (n = 4)

Fig. 1. PRISMA flow diagram. Flow diagram of search strategy and study selection. DB: database.

The kappa value between the two reviewers for the 10 selected articles was 0.81.

Effectiveness of prolotherapy compared with other therapies

Prolotherapy with dextrose compared to saline

The effectiveness of prolotherapy compared to saline was reported in five studies [15,16,18–20] (n = 246; prolotherapy group = 126, normal saline group = 120), which suggested that prolotherapy with dextrose significantly reduced the pain score from 6 months to 1 year (SMD, −0.44; 95% CI [−0.76 to −0.11]; P = 0.008; I² = 36%; Fig. 4A). However, there was no difference between the effects of both therapies during the other periods analyzed (SMD, −0.06; 95% CI [−0.51 to 1.35]; F = 0.003; I² = 88% at baseline to 1 month; SMD, −0.07; 95% CI [−0.37 to 0.23]; P = 0.66; I² = 0% at 1 month to 3 months). Sensitivity analysis using a single study removal method did not significantly change the pooled results. The therapeutic effect of prolotherapy was 33% lower (SMD, −0.29; 95% CI [−0.57 to −0.01]; P = 0.040) than the pooled estimate effect size (SMD, −0.44; 95% CI [−0.91 to −0.13]; P = 0.009) after omitting one trial [16].

Prolotherapy with dextrose compared to exercise

Two studies [15,18] (n = 128; prolotherapy group = 63, exercise group = 65) provided data on pain scores comparing prolotherapy and exercise. Compared to exercise, dextrose therapy significantly reduced the pain score from 1 month to 3 months (SMD, −0.44; 95% CI [−0.84 to −0.04]; P = 0.11; I² = 55%) and 6 months to 1 year (SMD, −0.42; 95% CI [−0.77 to −0.07]; P = 0.02; I² = 0%; Fig. 4B). However, there was no difference in the effects of both therapies during the baseline to 1-month-period (SMD, −0.42; 95% CI [−1.14 to 0.30]; P = 0.02; I² = 83%).

Prolotherapy with dextrose compared to PRP

Two studies [12,17] (n = 99; prolotherapy group = 51, PRP group = 48) reported data on pain scores comparing prolotherapy and PRP. Prolotherapy with dextrose had a therapeutic effect corresponding to that of PRP, and there was no significant difference from 1 month to 3 months (SMD, 0.05; 95% CI [−0.34 to 0.45]; P = 0.96; I² = 0%) and 6 months to 1 year (SMD 0.19; 95% CI [−0.20 to 0.59]; P = 0.34; I² = 0%; Fig. 4C).

Prolotherapy with dextrose compared to a steroid

Two studies [12,21] (n = 135; prolotherapy group = 68, steroid group = 67) suggested that prolotherapy with dextrose had a therapeutic effect comparable to that of steroids from 1 month to 3 months (SMD, 0.22; 95% CI [−1.27 to 1.70]; P < 0.001; I² = 94%) and 6 months to 1 year (SMD 0.45; 95% CI [0.57 to 1.47]; P = 0.39; I² = 88%; Fig. 4D).

DISCUSSION

Previous studies have reported that prolotherapy is effective for treating musculoskeletal pain. However, their analyses included a small number of studies, which was not thought to be enough to compare prolotherapy with common regimens such as corticosteroids or PRP [2,22].

Our principal findings revealed that prolotherapy with dextrose has a clear and positive effect on chronic musculoskeletal pain ranging from 6 months to 1 year. In comparison with saline injection or exercise, treatment with pro-
### Table 2. Characteristics of the Included Studies and Summary of the Preparations and Injection Details of Prolotherapy in the Retrieved Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>Intervention (number of patients)</th>
<th>Average age (yr)</th>
<th>Outcome measure(s)</th>
<th>Follow-up timing</th>
<th>Total number of prolotherapy injection &amp; interval</th>
<th>Prolotherapy regimen</th>
<th>Prolotherapy volume per dose</th>
<th>Prolotherapy injection technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabago et al., 2013 [15]</td>
<td>Knee OA</td>
<td>Dextrose (30) Saline (29) Exercise (31)</td>
<td>Dextrose 56.8 ± 7.9 Saline 56.8 ± 6.7 Exercise 56.4 ± 7.0</td>
<td>WOMAC KPS</td>
<td>Baseline, 5, 9, 12, 24, 52 weeks</td>
<td>3 (1, 5, 9 weeks. 3 basic doses but additional injections were allowed at 13, 17 weeks)</td>
<td>Intra-articular 25% dextrose 10 ml: 5 ml 50% dextrose + 5 ml 1% lidocaine</td>
<td>6 ml per 0.5 ml, up to 22.5 ml</td>
<td>Palpation at major tender tendon and ligament insertions through up to 15 skin punctures using a peppering technique, placing a possible total 22.5 ml of solution</td>
</tr>
<tr>
<td>Bertrand et al., 2016 [16]</td>
<td>Rotator cuff tendinopathy</td>
<td>Enthesis dextrose (27) Enthesis saline (27) Superficial saline (27)</td>
<td>Enthesis dextrose 53.8 ± 13.5 Enthesis saline 51.1 ± 9.2 Superficial saline 49.0 ± 11.9</td>
<td>VAS USPRS Satisfaction measure (0–10 scale)</td>
<td>For VAS at baseline, 3, 9 months For USPRS &amp; Satisfaction measure at baseline, 9 months</td>
<td>3 (0, 1, 2 months)</td>
<td>25% dextrose/0.1% lidocaine/saline</td>
<td>1 to 3 ml at primary injection site 0.5 ml at adjacent to primary injection area at 1 cm intervals</td>
<td>The supraspinatus, infraspinatus, and teres minor insertions, insertions on the coracoid process, were injected with the shoulder in neutral rotation. The biceps long head, subscapularis insertions, and inferior glenohumeral ligament were injected with the shoulder in various degrees of external rotation and abduction/adduction. Origins of the teres minor, teres major, and the posterior inferior glenohumeral ligament were injected posteriorly</td>
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<tr>
<td>Seven et al., 2017</td>
<td>Rotator cuff tendinopathy</td>
<td>Dextrose (60) Exercise (60)</td>
<td>50.19 ± 12.13 Ex</td>
<td>VAS SPADI WORC</td>
<td>Baseline, 3, 6, 12 weeks, and final follow up examination minimum of 1 year</td>
<td>3.6 ml 25% dextrose + 0.4 ml lidocaine</td>
<td>4 ml to the sub-acromial bursa</td>
<td>Shoulder in posterior lateral aspect of the acromion using 27 G needle</td>
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<td></td>
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<td></td>
<td>Exercise 46.31 ± 10.8</td>
<td></td>
<td></td>
<td>18 ml 15% dextrose + 2 ml lidocaine</td>
<td>Maximum 20 ml to 1. Supraspinatus, infraspinatus, teres minor insertions, pectoralis minor, coracobrachialis and biceps brachii insertions</td>
<td>Shoulder in neutral rotation using 27 G needle</td>
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<td>Should in external rotation and abduction/adduction using 27 G needle</td>
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<td></td>
<td>Injected posteriorly using 27 G needle</td>
</tr>
<tr>
<td>Yelland et al., 2004</td>
<td>Chronic low back pain</td>
<td>Dextrose + Exercise (28)</td>
<td>51.5 ± 10.6 Dextrose + normal activity 49.4 ± 10.4 Saline + exercise 50.0 ± 9.8 Saline + normal activity 50.9 ± 11.2</td>
<td>VAS Disability scores (Roland-Morris) VAS, disability scores (Roland-Morris)</td>
<td>Baseline, 2.5, 4, 6, 12, 24 months Primary outcome at 12 month Secondary outcome at 24 month</td>
<td>20% glucose + 0.2% lidocaine</td>
<td>3 ml at each site and a maximum of 10 sites</td>
<td>Injection site was tenderness in ligaments and broad tendinous attachments of lumbarosacral spine and pelvic girdle</td>
<td></td>
</tr>
<tr>
<td>Ersen et al., 2017</td>
<td>Chronic plantar fasciitis</td>
<td>Dextrose (26) Stretching exercise (24)</td>
<td>45.1 ± 6.7 Exercise 46.3 ± 7.8</td>
<td>VAS FAOS FFI</td>
<td>Baseline, 21, 42, 90, 360 days</td>
<td>3.6 ml 15% dextrose + 0.4 ml lidocaine</td>
<td>4 ml</td>
<td>Up to five different points, medial side of the heel and advanced under continuous ultrasound guidance into the proximal plantar fascia</td>
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<tr>
<td>Kim and Lee, 2014 [17]</td>
<td>Chronic plantar fasciitis</td>
<td>Dextrose (11) PRP (10)</td>
<td>37.8</td>
<td>FFI</td>
<td>Baseline, 2, 10, 28 weeks</td>
<td>2 (interval 2 weeks)</td>
<td>20% dextrose 1.5 ml + 0.5% lidocaine 0.5 ml</td>
<td>2 ml</td>
<td>Under US guidance, abnormal hypoechoic areas in the thickened proximal plantar fascia were targeted and the needle was inserted through the medial heel along the long-axis view (in-plane technique) toward the target area. Then, 2 ml of dextrose solution was injected using a peppering technique, which involved a single skin portal followed by 5 penetration of the fascia</td>
</tr>
<tr>
<td>Reeves and Hassanain, 2000 [20]</td>
<td>Knee OA</td>
<td>Total 111 knees in 68 patients. Dextrose Bacteriostatic water</td>
<td>N/A</td>
<td>VAS (at rest, with walking, with stair use)</td>
<td>Baseline, 6, 12 months</td>
<td>3 (every 2 months, and additional injections were allowed for dextrose group at 6, 8, 10 months)</td>
<td>10% dextrose + 0.75% lidocaine 9 ml</td>
<td>2 ml</td>
<td>Using 27 G needle via an inferomedial approach, tibiofemoral injection</td>
</tr>
<tr>
<td>Reeves and Hassanain, 2000 [19]</td>
<td>OA in thumb and finger</td>
<td>Dextrose (11) Bacteriostatic water (14)</td>
<td>64.5 ± 9.2</td>
<td>VAS (at first step in the morning)</td>
<td>Baseline, 6 months</td>
<td>3 (every 2 months)</td>
<td>10% dextrose + 0.075% xylocaine in bacteriostatic water</td>
<td>0.5 ml at each site</td>
<td>Using 27 G needle, All symptomatic DIP, PIP, thumb CMC joints were injected at the joint line laterally and medially until firm resistance was felt</td>
</tr>
<tr>
<td>Uğurlar et al., 2018 [12]</td>
<td>Chronic plantar fasciitis</td>
<td>ESWT (39) Dextrose (40) PRP (39) Steroid (40)</td>
<td>39.2</td>
<td>VAS (the first step in the morning)</td>
<td>Baseline, 1, 3, 6, 12, 24, 36 months</td>
<td>3 (every 1 week)</td>
<td>1 ml bupivacaine 5 mg/ml + 5% dextrose 3 ml + 0.9% normal saline 6 ml bupivacaine 5 mg/ml</td>
<td>Under US guidance, injection was done into the site of maximal tenderness</td>
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Table 2. Continued

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<td>Jahangiri et al., 2014 [21]</td>
<td>OA in the first carpometacarpal</td>
<td>Dextrose (30) Corticosteroid (30)</td>
<td>Dextrose 63.9 ± 9.4 Corticosteroid 63.3 ± 10.1</td>
<td>VAS (pain intensity of tenderness, pain on joint movement) Hand function (self-administered questionnaire) HAQ-DI about eating, gripping, dressing Strength (later al pinch grip)</td>
<td>Baseline, 1, 2, 6 months (every 1 months)</td>
<td>20% dextrose 0.5 ml +2% lidocaine 0.5 ml</td>
<td>1 ml</td>
<td>A 25 G needle was inserted toward the ulnar side of the extensor pollicis brevis and just proximal to the base of the first metacarpal in the snuffbox</td>
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Corticosteroid injection has been widely used as it is known to be effective in the treatment of musculoskeletal disorders. In vitro studies have shown that corticosteroids have therapeutic effects on the tendon and the surrounding matrix molecules, and granulation tissue production, in addition to inflammatory suppression [23]. However, such positive therapeutic effects of corticosteroids may exist only in the short term [24], Ugalar et al. [12] reported that the effects of corticosteroid injection were an effective treatment in the first 6 months, but lost its effectiveness after the first 6 months. The effect of pain relief in corticosteroid injection was seen within 3 to 12 months. In another study, Jahangiri et al. [21] compared the effects of corticosteroid injection and prolotherapy in patients with first carpometacarpal osteoarthritis and reported that the corticosteroid injection group had better results of pain score at 1 month. However, after 2 months, prolotherapy had a more favorable outcome than corticosteroid injection. Although not shown in our study, three RCTs reported only minor transient complications such as mild to moderate pain and self-limiting bruising after prolotherapy. We found that PRP and dextrose prolotherapy were shown to be effective for treating degenerative conditions and injuries. Both PRP therapy and prolotherapy commonly have regenerative therapeutic properties, but the central concentrations of growth factors directly to a lesion [26-27]. In contrast, corticosteroid injection has no serious side effects and is effective, safe, and sustainable [16]. In this study, Jadidi et al. [32] reported that platelets are separated from other components of blood based on their ability to adhere to the surface of cells and are further concentrated [33]. The occlusion of blood components and further concentrated [33]. This occurs through a centrifuge process, in which platelets are isolated from the other cell components of blood based on their ability to adhere to the surface of cells and are further concentrated [33].
Further concentration of platelets occurs with subsequent centrifuge cycles [34]. As such, several steps are needed to prepare PRP, whereas the preparation of prolotherapy is simple. And PRP involves an invasive procedure (i.e., blood drawing) and lacks an optimized standardized protocol. In this regard, prolotherapy can provide more convenience to both patients and treatment providers.

Of the ten papers included in the study, nine papers showed generally positive results of achieving pain relief and patient satisfaction regardless of the injection site. Yelland et al. [18] reported that prolotherapy was not more effective than injections of normal saline for low back pain. Nevertheless, participants exhibited marked and sustained improvements in their pain and disability, even with saline injections. They assumed that these therapeutic effects could be achieved by other factors such as patients were enrolled in a trial during severe pain and then spontaneously recovered naturally, or by the therapeutic effect by direct needling of entheses, or the placebo effect by clinical visits.

In the case of using physiotherapy as a control group [13, 14], the positive result from the comparison with prolotherapy was within expectations because injection carries a strong placebo effect, which usually leads to a superior response to the noninvasive treatment.

The present study mainly analyzed the pain measurement outcomes, and functional improvement measurements were not considered. Among the RCTs, investigations of functional improvements were conducted in eight studies. Six studies reported that the prolotherapy group showed a moderately superior therapeutic effect. In particular, prolotherapy was found to be more effective than exercise from one month after treatment. It was also found to have a similar effect to steroids or PRP one month their physiological size [33]. Further concentration of platelets occurs with subsequent centrifuge cycles [34]. As such, several steps are needed to prepare PRP, whereas the preparation of prolotherapy is simple. And PRP involves an invasive procedure (i.e., blood drawing) and lacks an optimized standardized protocol. In this regard, prolotherapy can provide more convenience to both patients and treatment providers.

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had a significant improvement in function compared to the control group [13,15,17,19–21]. One study showed functional improvement at 90 days after treatment, but after 360 days, both the prolotherapy and control groups showed similar results [14]. In one study, no significant improvement was noted in any of the groups at the end of the follow-up period [12]. However, unlike other studies which used a dextrose concentration of 10% or higher, this study only used a 5% concentration. When used clinically, dextrose concentrations higher than 10% are partly affected by inflammatory mechanisms, while concentrations less than 10% are considered noninflammatory [35,36]. Considering this, it is possible that a low concentration of dextrose could have affected the therapeutic effect. Although the degree of pain reduction and functional improvement is not completely consistent, there seems to be a correlation

**Fig. 4.** Forest Plot; (A) saline (B) exercise (C) PRP (D) steroid. Forest plot diagram showing comparisons of VAS for Pain Composite between dextrose prolotherapy and the reference treatments 6 months–1 year. (A) Dextrose vs. Saline on VAS for pain composite 6 months–1 year. (B) Dextrose vs. Exercise on VAS for pain composite 6 months–1 year. (C) Dextrose vs. Platelet-rich plasma on VAS for Pain Composite 6 months–1 year. (D) Dextrose vs. Steroid on VAS for Pain Composite 6 months–1 year. PRP: platelet-rich plasma, VAS: Visual Analog Scale, Std. Mean difference: standardized mean difference, IV: weighted mean difference, CI: confidence interval, SD: standard deviation.
between the two in the studies that were included in this meta-analysis.

Although there were several positive aspects of our study, there are some limitations. First, despite recent studies being added, the number of trials eligible for inclusion in the meta-analysis was limited. Since the results regarding prolotherapy corresponding to the effects of corticosteroids and PRP were derived by analyzing only two studies, additional studies are needed. Second, there is heterogeneity in the pooled analyses; this is likely attributable to multiple factors, including differences in patient characteristics, control treatment, study design, injection protocol methods, dextrose concentrations, follow-up duration, and outcome assessment methods. A limited number of studies and heterogeneity have inhibited more detailed meta-analyses of subgroups. Third, due to a lack of a uniform longer-term follow-up duration across the studies, pooling of results could only be done with data collected between 6 months and one year of follow-up. Considering that prolotherapy is hypothesized to work by healing and regeneration over several months, reported results of effects may underestimate long-term benefits. Therefore, further studies (including cohort studies) are needed to evaluate the long-term effects. Fourth, since prolotherapy has been shown to have comparable effects to steroid injection and PRP, further studies should be conducted regarding cost effectiveness. Jahangiri et al. [21] compared prolotherapy and corticosteroids and mentioned that there was no significant difference in cost. In previous study, prolotherapy was more effective [14], and has a better cost advantage compared to PRP [37].

In the future, subgroup analysis should be performed to identify patients who respond most favorably to prolotherapy. There are several ways in which treatment strategies can vary; for example, dextrose concentrations/volumes may differ, the interval and total duration of treatment may differ, and the site of injection (intra- or extra-articular areas) may differ. Since there are no clear criteria or standard treatment, this should be discussed in the future. Reducing pain, improving functionality, and increasing patient satisfaction provide a solid foundation for further research in attempt of treatment standardization.

In conclusion, dextrose-based prolotherapy has been shown to have a positive and significantly beneficial effect for patients with chronic musculoskeletal pain, ranging from 6 months to 1 year. There is evidence that dextrose-based prolotherapy has a better therapeutic effect than exercise, and that it has a similar effect compared to PRP and steroid injection. Adequately powered, longer-term trials with uniform endpoints are needed to better elucidate the efficacy of prolotherapy.

ACKNOWLEDGEMENTS

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conceptualization: Geonhyeong Bae, Yunhee Lim. Data curation: Geonhyeong Bae, Sangseok Lee, Woo Yong Lee, Yunhee Lim. Formal analysis: Geonhyeong Bae, Yunhee Lim. Funding acquisition: Yunhee Lim. Writing - original draft: Geonhyeong Bae, Yunhee Lim. Writing - review & editing: Suyeon Kim, Sangseok Lee, Woo Yong Lee, Yunhee Lim. Supervision: Yunhee Lim.

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Lumbar disc herniation (LDH) commonly causes low back pain (LBP) and radiculopathy. LDH often resolves over time with a spontaneous resorption rate of 60% or above [1]. Therefore, the consensus for treating patients with LDH is to offer conservative treatment first and then surgical intervention for non-responders [2].

One conservative treatment used for LDH is transforaminal epidural steroid injection (TFESI). TFESI is a method used to deliver steroids and local anesthetics into the epidural space through the spinal neural foramen. Numerous reports and extensive reviews have demonstrated the diagnostic efficacy of TFESI as well as its effectiveness in LBP and relief from radiculopathy pain [3]. However, various complications have been reported as the use of TFESI has increased. Some classic complications of TFESI include intravascular injections, vascular trauma, epidural hematoma, and neural damage [4]. There are also case reports documenting paraplegia—a serious complication—following TFESI. Most of the reported paraplegia cases were due to spinal cord ischemia from a vascular injury or a particular steroid embolism [5].

We encountered a patient whose severe LBP and radiating...
pain induced by postural changes prevented the assessment with imaging modalities. Thus, TFESI was performed to relieve the patient’s pain. Here, we report this case as the patient developed paraplegia immediately after TFESI.

**CASE REPORT**

The patient has provided written informed consent for publication of the case and associated images. This case report follows the CARE (CAse REport) guidelines [6].

A 70-year-old woman came to the emergency room (ER) complaining of severe LBP. The patient was not able to walk, and she was in the left lateral decubitus position with lumbar flexion. The patient’s numerical rating scale (NRS, 0 being no pain and 10 being the worst pain imaginable) score for LBP was 6/10, but when asked to perform lumbar extension or move to a supine position, the NRS score for LBP increased to 9/10, with development of left buttock pain and radiating pain in the left thigh. The patient had undergone a posterior lumbar interbody fusion at L2–S1 for a herniated nucleus pulposus 2 years prior to the ER visit. The pain dissipated after the surgery; however, the patient started to experience intermittent recurrences of LBP 1 year after. Three days prior to hospitalization, the patient was unable to lie in the supine position even when sleeping owing to severe LBP and buttock pain.

The patient’s height was 154 cm, and her weight was 65 kg. The vital signs included blood pressure 150/90 mmHg, body temperature 36.5°C, pulse rate 86/min, and respiratory rate 20/min. Due to the complaint of extreme pain with any change in position, it was necessary to perform a neurological examination on the patient; therefore, the orthopedic surgeon quickly performed the possible tests in the left lateral decubitus position as desired by the patient. However, during the neurological examination, the patient continued to complain of pain. A neurological examination to assess the motor power revealed left ankle dorsiflexion grade 4/5, left big toe dorsiflexion 4/5, left knee extension 4/5, and left hip flexion 4/5, indicating motor weakness. The patient also had a sensory deficit throughout the left leg and complained of numbness in the left thigh. The patient showed an absence of the Babinski reflex, an ankle jerk reflex scale measurement of 2+, and a knee jerk scale measurement of 3+. The right leg did not show any motor weakness or sensory deficit. The patient did not have urinary incontinence or saddle anesthesia, and the anal sphincter tone was retained.

However, we recognized that the patient’s spinal disease may be serious due to the patient’s history of previous surgery, complaint of severe pain, and abnormal findings on neurological examination of the left lower limb. Consequently, the orthopedic surgeon explained that the disease was severe, and that the patient may require surgery, and additional imaging tests. In our hospital, magnetic resonance imaging (MRI) can only be performed in the supine position; however, as the patient was in a very nervous state due to pain and complained of pain even when moving on the bed or changing position for examination, it was determined that pain control was necessary for additional examination; 100 μg of fentanyl (50 μg/ml) was then administered intravenously. However, the pain relief was inadequate and the patient was unable to change position. Since additional examinations could not be performed, the patient strongly requested priority pain relief before additional imaging examinations.

Our anesthesia and pain medicine department was asked to control this patient’s pain. We also considered that the patient may be at high risk for complications with a nerve block because the type of spinal disease was not clearly identified, the state of the nerves could not be ascertained, and abnormal findings were already observed in the neurological examination. However, we understood the urgency of the imaging test; hence, we explained the risk of the procedure and the possibility of side effects to the patient and then planned the pain relief procedure. Given the patient’s L2–S1 vertebral body fusion with possible adjacent segment disease, we chose to perform a TFESI through the left L1–2 neural foramen.

The procedure was conducted 3 h after the patient arrived at the ER, with the patient kept in her preferred left lateral decubitus position with lumbar flexion. C-arm fluoroscopy was performed, and the typical lateral view angle was used in order to obtain the anteroposterior view. A fluoroscopic lateral image indicated a kyphotic deformity at the L1 vertebral body, likely caused by osteonecrosis.

After the skin had been sterilized, 2 ml of 1% lidocaine was administered for local anesthesia. To create an oblique view in order to visualize the left L1–2 neural foramen, the C-arm angle was turned 20° to the left from the anteroposterior view. A 20-gauge short bevel nerve block needle was inserted until the needle tip reached the inferior margin of the L1 lumbar pedicle, and the lateral view was checked after the needle tip reached the middle of the pedicle. In the lateral view, the needle tip was located immediately before

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reaching the dorsal periosteum of the L1 vertebral body; 2 ml of contrasting agent was used to confirm that the location of the needle tip was appropriate for the epidural injection (Fig. 1). No blood vessel contrasting was observed. During the procedure, the contrast agent did not disappear rapidly due to blood or cerebrospinal fluid flow. The contrast agent showed a pattern of spreading along the epidural space.

A 6 ml mixture containing 10 mg of 0.5% bupivacaine (5 mg/ml), 3 ml of normal saline, and 5 mg of dexamethasone (5 mg/ml) was injected slowly.

Five minutes after the injection, the patient’s LBP NRS score decreased to 2/10. A neurological examination showed no change in motor or sensory functions compared to pre-injection. Her vital signs were as follows: blood pressure, 124/68 mmHg; body temperature, 36.5°C; pulse rate, 70/min; and respiratory rate, 16/min. Although the blood pressure was lower than that before the procedure, it was within the normal range, and this was judged to be due to the reduction in pain. When epidural nerve block is performed, neurological changes and changes in vital signs may occur slowly, and thus additional patient monitoring was necessary. However, after further discussions with an orthopedic surgeon, it was decided that the imaging test should be performed quickly. The patient was able to lie supine with reduced pain and was sent for an MRI. During the MRI scan, the patient reported acute paraplegia and a complete loss of motor and sensory functions in both legs including the sensation around the anus. The patient also lost the anal reflex and bulbocavernous reflex. The vital signs were as follows: blood pressure, 118/70 mmHg; body temperature, 36.6°C; pulse rate, 70/min; and respiratory rate, 18/min.

We assessed the situation at the time of the procedure, and contrasted images were reviewed to determine the cause of paraplegia. The operator who had performed TFE-SI judged that the contrast medium had spread to the epidural space. The possibility of intrathecal injection could not be completely ruled out. However, we injected bupivacaine at a low concentration, so the complete loss of motor sensory function as seen in this patient was determined to be unlikely. We also speculated that the progress of cauda equina syndrome (CES) may have been accelerated due to the effect of the pressure or volume when the drug was injected. It was also impossible to completely rule out the possibility of a hematoma being produced due to blood vessel damage caused by the needle. We could obtain the patient’s MRI results. Upon assessing the MR images, we found that the patient’s conus medullaris was located above the L1 body and CES occurred due to L1–2 LDH. There was no indication of any cord injury (Fig. 2).

An emergency decompression surgery was performed 1 h after the paraplegia developed. The L1 lamina was excised, and decompression and discectomy on both sides were performed. In order to resolve the kyphotic deformity, posterior lumbar fusion was also performed at T11-L1 (Fig. 3). The surgeon confirmed that the dural sac was strongly compressed by the disc at the L1–2 level during surgery. In addition, there was slight bleeding around the disc at L1–2. The situation was determined to be inconsistent with nerve compression due to bleeding. However, it was difficult to clearly identify the cause of this bleeding. It was not possible to specify whether bleeding occurred due to the TFESI procedure, or whether blood vessel damage occurred due to pressure applied to the inner portion of the spinal canal by the disc.

The patient’s paralysis did not resolve after the surgery.
The patient was hospitalized for 6 weeks, and repeated neurological examinations were conducted to assess signs of recovery. At week 6, no change in motor function, and only a mild recovery of sensory function were observed. There was a recovery of fine touch and proprioception in both thighs, but the bladder function did not recover. The patient was transferred to a rehabilitation hospital at her request, and she agreed to come in for a 6-month follow-up. At the follow-up visit, the patient had a 3/5 of muscle strength grade and did not have any voiding difficulties. However, numbness throughout both legs persisted.

**DISCUSSION**

Recently, TFESI has been widely used in patients with various spinal diseases. TFESI is particularly useful for pain relief in patients with LDH. However, several complications caused by TFESI, including infection, vascular injury, hematoma, intravascular drug injection, nerve damage, embolism, and paraplegia, have been reported. To prevent the occurrence of these complications, we need to understand the patient’s disease state as early as possible and decide on the most appropriate treatment plan. The process of making this judgment is facilitated by the patient’s medical history, neurological examination, and imaging tests. Among these, the most helpful information is provided by the MRI examination [2].

It is very rare to encounter a patient whose posture change is completely impossible due to extreme pain, as was the case with our patient. As a result, the patient was unable to lie in a supine position, making imaging tests completely impossible. In general, if a patient’s symptoms are severe and neurologic deficit is involved, imaging tests are performed first. TFESI is then performed to facilitate the diagnosis and treatment of the patient. However, we were asked to perform a TFESI for the purpose of performing an imaging test without being provided with any imaging test results prior to the procedure. The patient’s pain was not controlled even with narcotic analgesics. The initial neurological examination did not prompt us to suspect CES. Under the opinion that the MRI was necessary even for surgery, we proceeded with TFESI. At that time, the patient complained of extreme pain and had abnormal neurological examination findings. If a patient shows CES or neurological symptoms are progressing rapidly, surgical treatment should be selected [2].

According to the results of the MRI, which was per-
formed after TFESI and the patient’s pain had been alleviated, it was presumed that the patient had already had Kümmler’s disease or spondylodiscitis. Further, a kyphotic deformity due to osteonecrosis was progressing at the L1–2 level. In addition, severe LDH of L1–2 could cause severe pain and paralysis. It was presumed that the patient was avoiding paralysis by keeping the spinal canal wide via lumbar flexion [7]. So, it seems that the patient felt severe pain and refused to adopt a position of back extension. This patient developed paraplegia after TFESI, as the disease rapidly worsened. The relationship between CES and TFESI in this patient is not clear. However, there are several possible causes that may have led to CES in this patient.

First, CES may have occurred due to a rapid increase in pressure within the epidural space as the drug was injected during the procedure. According to a study by Usubiaga et al. [8], pressure in the epidural space can increase from –10 cmH₂O to a maximum of 65 cmH₂O when 10 ml of 2% lidocaine is injected. In particular, pressure in the epidural space was higher in elderly patients, and high levels of pressure could be maintained up to 2 min after injection of the drug. The patient in our case had an epidural space volume that was too small for her to tolerate pain without adopting the lumbar flexion position. For this reason, it was thought that the pressure created by drug injection into the epidural space acted more strongly. If such an elderly patient is expected to have high pressure in the epidural space due to severe LDH, a small amount of the drug should be injected as slowly as possible.

Alternatively, it is possible that blood vessel damage occurred. The radicular artery enters the intervertebral foramen along the nerve root. The probability of the radicular artery being in the upper portion of the intervertebral foramen is twice as high as that of it being in the lower portion [9]. The patient in our case had undergone posterior lumbar interbody fusion surgery at the L2–S1 level, and it was assumed that severe LDH occurred at the L1–2 level. We predicted that it would be difficult for the needle to enter the lower portion of the foramen while performing TFESI at the L1–2 level and instead inserted the needle into the upper portion of the foramen. Although the blood vessels were not imaged using a contrast agent, the possibility that blood vessel damage occurred cannot be excluded. In addition, the radicular artery or internal vertebral venous plexus may have been damaged as the pressure in the epidural space increased as mentioned previously [10]. It is possible that this vascular injury contributed to the occurrence of CES.

A third reason, post-procedural changes in posture due to pain relief may have exacerbated the disease. The lumbar flexion posture can exacerbate LDH by applying pressure within the disc. However, the lumbar flexion position increases the capacity of the spinal canal [7]. As mentioned previously, the patient had already experienced a serious LDH condition that caused CES, but her position may have reduced the pressure applied to the dural sac by increasing the diameter of the spinal canal with lumbar flexion. However, after TFESI, the patient was able to lie in the supine position because back extension was possible. At this time, the capacity of the spinal canal would have decreased. As a result, it is expected that the dural sac was strongly pressed and CES occurred immediately. There is an existing case report of CES that progressed according to a similar mechanism [11]. In the reported case, the patient was diagnosed with spinal stenosis, and an MRI scan was difficult due to the severe pain experienced by the patient when in the supine and back extension position. Hence, to proceed with the examination, the patient was sedated with propofol while lying in the supine position. Subsequently, an MRI scan was performed and CES occurred.

Before TFESI is performed, it is important to determine the patient’s neurological condition, disease, and cause of pain via MRI. However, as was observed in our case, if a posture change is impossible and the imaging test cannot be performed, it can be challenging to effectively treat the patient. Recently, MRI equipment capable of performing examinations in various postures such as sitting or standing has been developed and used [12]. The use of such equipment is thought to be helpful for imaging tests in patients who are unable to maintain a supine position due to pain.

However, if such equipment is unavailable, the cause and severity of pain, as well as the risk of the procedure, should be determined by reviewing the patient’s medical history and performing a neurological examination. In patients with LDH, lumbar motion limitation, resting pain, and deformity are red flags [13]. In addition, patients who experience leg pain during lumbar extension have a poor prognosis [14]. When TFESI is performed on high-risk LDH patients, a thorough assessment of positional- and motion-based pain characteristics, including a neurological examination, is necessary. Patients should be informed and educated about the risks of exacerbation of their existing disease with positional changes after pain relief from
TFESI. In addition, when performing TFESI on high-risk LDH patients, physicians should be prepared for any emergency.

In our case, the patient developed CES due to L1–2 level LDH. Fortunately, the patient’s conus medullaris was located above the L1 body; however, the conus medullaris is usually located between T12 and L2. Conventionally, if the dural sac of the L1–2 level is compressed, not only CES but also conus medullaris syndrome (CMS) can occur. In both CES and CMS, radiating pain, as well as motor and sensory dysfunction of the lower extremities, can occur, and bladder dysfunction and saddle anesthesia may be seen. Since both syndromes show similar symptoms, it is difficult to distinguish them based on clinical features alone; however, they are easily distinguishable via MRI. Additionally, treatment of both syndromes commonly requires emergency decompression surgery [15]. If CMS would have occurred, recovery would have been more difficult even if emergency decompression surgery had been performed.

We performed TFESI without an accurate initial assessment of the patient’s disease state and observed paraplegia in this patient after TFESI had been performed. It is important to accurately evaluate the patient before this procedure, establish a correct treatment plan, and safely perform the procedure using methods designed to reduce the occurrence of complications. In addition, it is important to explain the risks and possible complications of the procedure to the patient, so that they are able to prepare for the possibility of experiencing serious complications. Even when extreme care is taken, complications may occur after the procedure. If such a complication occurs, the rapid identification of its cause and a prompt response greatly affect patient recovery.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS


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Spinal cord stimulation (SCS) has been used to treat various chronic neuropathic pain conditions for many decades [1]. SCS has been reported to be a relatively safe and reversible procedure with several complications due to minimally invasive properties. Common complications associated with SCS include lead migration, connection failure, lead breakage, pain at the implant site, seroma formation, and infection [2]. Catastrophic complications, including breakdown of the tissue overlaying implant site and extrusion of the device through the skin are possible, but very rare [3]. Pacemakers, which have a structure similar to that of the implantable pulse generator (IPG) component, have been reported to extrude out of the chest [4].

We report a case that unexpected extrusion of the IPG of SCS was promptly identified and successfully removed without any further adverse complications. Prior to this report, we received prior written informed consent for publication from the patient.

**Background:** Despite significant technological advances in the implantable pulse generator (IPG), complications can still occur. We report a case that unexpected extrusion of the IPG of spinal cord stimulation (SCS) was promptly identified and successfully removed without any complications.

**Case:** After a car accident 4 years ago, a 55-year-old male who was diagnosed with complex local pain syndrome in his right leg. The SCS was inserted with 2 leads, with the IPG being implanted in the right lower abdomen region. Four years later, he developed extrusion of the IPG from his abdominal region. This unexpected extrusion may have been related to pressure necrosis caused by continued compression of pocket site where a belt was frequently tied. The IPG and the leads were successfully removed without infection occurring.

**Conclusions:** To prevent unexpected extrusion of IPG, it is necessary to consider in advance whether the pocket site is pressed against the belt.

**Keywords:** Complex regional pain syndrome; Devices; Necrosis; Neuropathic pain; Spinal cord stimulation.
A 55-year-old male with a height of 169.2 cm and a weight of 71.5 kg, who was diagnosed with complex regional pain syndrome in the right leg, was visited our pain clinic to evaluate SCS. He was in a car accident four years ago. There were no particular fractures at the time of the accident, and 3 months later, despite proper treatment, he suffered from refractory, persistent pain, edema, temperature and color changes, and hyperhidrosis of his right leg and foot. He was taking various oral medications (acetaminophen, tramadol, gabapentin, duloxetine, baclofen, and oxycodone) and had undergone several interventions (lumbar transforaminal epidural steroid injection, lumbar sympathetic ganglion block, and lumbar sympathetic alcohol neurolysis), but there was no significant pain relief. He complained that his baseline leg pain was 10 out of 10 in severity. The findings of magnetic resonance imaging, electromyography with nerve conduction study, bone densitometry, and 3-phase bone scan were non-specific. Digital infrared thermographic imaging of the lower extremities showed a body temperature 1–2.5°C lower in the right leg compared to the left leg.

Prior to the trial implantation of the SCS device, he conducted a structural interview and the Minnesota Multiphasic Personality Inventory by a psychologist. He was also trained about the system, its use, and the trial and implant procedures using printed materials and videos.

After he was admitted to our hospital and had agreed to the operation, he was offered an SCS trial using a lead delivery system device (Epiducer ™, St. Jude Medical Neuro modulation Division, USA). After the skin was anesthetized, a 14-gauge needle, a steerable guide wire was inserted into the L4/L5 epidural space using fluoroscopy. The needle was then removed, and the Epiducer ™ was threaded over the guidewire and into the epidural space. After finding no regurgitation of cerebrospinal fluid or blood, the inner dilator and guide wire are removed. The S-Series paddle lead (St. Jude Medical Neuromodulation Division) was inserted via the Epiducer ™, and the lead tip was located at the T10 to T12 level. The test simulation was performed in a range of 2 to 1,200 Hz, with typical pulse frequencies of 40 to 60 Hz. Stimulation covered the patient’s right leg and the dorsum of his foot. The lead was buried in the subcutaneous tissue. During the SCS trial, the pain decreased to 4 out of 10. He reported greater than 50% relief of pain in his right leg. After 1 week of trial stimulation, the implantable pulse generator (IPG) was implanted. Before the operation, the implantation and incision sites were examined and marked in a sitting or standing position, the subcutaneous pocket site for the IPG (Proclame™, St. Jude Medical Neuromodulation Division) was made at the right lower abdominal wall. The IPG was implanted 2 cm deep in the right abdominal subcutaneous pocket site. The SCS was functioning well and showed no immediate post-surgical complications.

Two months later, he was generally satisfied with the pain relief; however, he reported that the stimulation did not come to the medial and sole of the foot, and hoped to reduce the pain in the region using another cylindrical lead (Octrode, St. Jude Medical Neuromodulation Division) for spinal cord stimulation. Therefore, we performed an additional operation to insert the lead, and the lead tip was located at the L1-L2 level (Fig. 1). He reported that electrical stimulation was smooth on all parts of his right leg and foot, and he experienced marked pain relief. The patient visited the clinic for follow-up evaluations every 1-2 months after the procedure. He was very satisfied with the pain relief on his right leg. In daily life, he paid special attention not to press the IPG insertion site when sleeping or

![Fig. 1. The lead tips were located at the T10-T12 (paddle lead) and L1-L2 (cylindrical lead) level on simple X-ray L-spine anterior-posterior view.](image-url)
During activities, however, he was engaged in agriculture and was always doing hard work with his body bent in a sitting position. He occasionally noted a foreign body sensation in the IPG pocket site when wearing a belt. Sometimes, when he tightened his belt, he complained that the skin of the IPG site felt under pressure.

At a routine follow-up, he complained of wound site erosion, and a metal piece was exposed from his lower abdominal wall for 2 days. He denied having fevers and chills. On examination, the IPG had moved approximately 3 cm below the pocket, and a 0.5 cm area of metal part was protruding from his right lower abdominal wall. There was erosion around the entry and exit points of the IPG, with apparent healing of the tissue beneath. There was no discharge from the extrusion site from the eroded areas, and microbiological cultures were taken from several points around that region (Fig. 2). The pocket did not show any signs of active inflammation or infection. The IPG test revealed that the device's functional values were completely within normal ranges. After obtaining written informed consent, the patient had the stimulator leads and the IPG removed. The lower abdominal pocket site was thoroughly cleaned and debrided after the IPG removal, and the wound was sutured (Fig. 3). After surgery, the patient recovered uneventfully. The stimulator leads and the IPG removed during surgery were sent for aerobic and anaerobic culture, which returned back negative. The patient was prescribed cefazoline as postoperative antibiotic for 14 days. After removal of IPG, his right leg pain was 8-9 out of 10 in severity, as the pain was managed with only oral medication and several conservative interventions. With all the risk of infection removed and stable, we decided to perform re-implantation of the SCS device later.

DISCUSSION

SCS has been an effective surgical procedure for improving suffering among patients with chronic neuropathic pain. However, several complications can occur despite significant technological advances in the IPG, with significant decreases in both size and weight, and rechargeable capabilities.

Complications of SCS have been reported to have an incidence of 30–40% in several studies [5, 6]. Its complications are divided into three main categories: hardware-related, biological, and programming or therapy-related. Hardware-related complications include lead fracture or disconnection reported incidence of 5–9%, lead migration reported incidence of 0–27%, and IPG failure in around 1.7% [1, 7]. Biological complications include pain at the implant site, allergic reaction, IPG seroma, infection, epidural fibrosis, epidural hematoma, dura puncture-related headaches and more serious nerve damage, including spinal cord injury and paralysis [8, 9]. Programming or therapy-related complications include loss of paresthesia and painful

Fig. 2. The implantable pulse generator was extruded at the lower abdominal pocket site.

Fig. 3. The lower abdominal pocket site was thoroughly cleaned and debrided after implantable pulse generator removal, and the wound was sutured.
or unpleasant paresthesia. These are less threatening and can usually be resolved through programming, although on rare occasions can be removed due to therapy failure [10].

Among the several complications mentioned above, IPG extrusion is a hardware-related complication, and it is a very rare complication of SCS. In two cases, IPG extrusion was reported after implantation in the gluteal area [3,11]. In one of these cases, the patient was a truck driver who had been driving for a long time for three months, causing skin erosion in the buttocks and extruding the IPG. In the other case, an extrusion of the IPG in a sacral stimulator was due to rapid weight loss after the patient underwent gastric bypass surgery. Our report is the first case of extrusion after implantation of the IPG of a spinal cord stimulator into the abdominal wall. In a case similar to our report, there are multiple case reports of pulse generator extrusion of a pacemaker [4,12]. They were caused by the skin eroding around the IPG insertion. The incidence of skin erosion due to the underlying pacemaker generator has been estimated to be approximately 0.8%. Factors predisposing skin erosion are the presence of a thin subcutaneous fat layer, tissue fragility in old-age patients, abrasive action exerted on the skin from external agents, pressure exercised from the device on the subcutaneous tissue and possible infections of the site [13].

The patient had been doing well after the operation. Occasionally the patient complained of the discomfort of the IPG insertion when wearing a belt. The IPG were sutured to the subcutaneous fat layer of the abdominal wall to fix at the initial insertion site, but it seems that a tear occurred at the suture site. As a result, the IPG migrated downward from the initial insertion site, and it seems that the downward migration was a little worse due to the compression of the belt. Skin erosion occurred due to compression of the belt, and the IPG was extruded through this area. Whenever the patient wore a belt, he complained of discomfort due to the constant pressure on the IPG pocket site. We should have carefully observed skin erosion during follow-up. The early stages of skin erosion can develop exposure of the pocket site, and even IPG migration and extrusion. If the IPG size and configuration are not appropriate, excessive pressure can be placed on the subcutaneous tissue, and improperly sized pockets may result in the development of infection and dysfunction of the IPG [14]. With a careful follow-up as well as a clear understanding of potential complications and a careful approach to device selection can minimize the incidence of complications. It is important to identify early signs of erosion before the device damages the skin. If the skin is not damaged, surgical modification of the pocket is often necessary to prevent contamination and infection of the device. However, if the hardware is exposed, it should be assumed that the device is contaminated, and treatments generally involve a much more complicated procedure to remove all devices, including IPG and leads [15].

In conclusion, extrusion of the IPG from the pocket site is very rare. In order to prevent this rare complication, prior to permanent SCS insertion, the clinicians should fully consider the patient’s age, occupational hazards, and daily life habits that could cause excessive pressure on the IPG. And the skin of abdominal wall should be inspected carefully at the site of the intended pocket, and the belt-tightening area should be examined in advance to see if all the SCS components, such as the IPG, will not be pressed by the belt. A deep pocket (about 2–3 cm depth), instead of just a pocket under the skin, should be considered. In addition, it is necessary to educate the patient not to habitually touch the IPG insertion site with a sense of foreign body.

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**CONFLICTS OF INTEREST**

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INTRODUCTION

Pressure injury, also called pressure ulcer or pressure sore, is defined as localized cellular necrosis caused by constant compression between external materials and bony prominences. The severity of pressure injury varies from erythema to tissue destruction. The National Pressure Injury Advisory Panel (NPUAP) defines a 4-stage classification system as follows: Stage 1, non-blanchable erythema of intact skin; Stage 2, partial-thickness skin loss involving...
epidermis or dermis, such as abrasion, blister, or shallow crater; Stage 3, full-thickness skin loss involving damage or necrosis of subcutaneous tissue; and Stage 4, full-thickness skin loss with extensive destruction, tissue necrosis, and damage to muscle, bone, and supporting structures [1].

Perioperative patients are at risk of developing pressure injuries since anesthetic agents interrupt normal relaxation and contraction of blood vessels and reduce perfusion at the site of the bony prominence. The patient’s surgical position is another factor that increases incidence of pressure injury, as anatomical structures such as nerves, muscles, and tendons are extended or compressed for a long period, which interferes with capillary perfusion. The incidence varies from 3.7% to 23.8% [2,3] in surgical patients, which may depend on the patients’ characteristics (age, comorbidities, etc.), type of surgery, injury stage, and time after surgery when the injury was discovered.

Previous literature have typically reported stage 2 pressure injuries or higher as these injuries are associated with bacterial infections, osteomyelitis, and squamous cell carcinoma and contribute to increased mortality [4]. However, stage 1 pressure injury should not be overlooked as it may lead to patient discomfort, pain, prolonged hospital stay, and subsequent pressure ulcer development [5,6]. Although surgical factors, such as type of procedure and positioning, are important factors associated with pressure injury, most previous studies did not focus on a specific type of surgery or surgical position. In our clinical experience, pressure injuries more frequently occurred in patients undergoing spinal surgery than in patients undergoing other surgeries. Spinal surgeries are mostly performed in a prone position, and many of them are for spinal fusion, which usually cause a considerable amount of bleeding and are associated with prolonged surgery duration, which are associated with the known perioperative risk factors for pressure injury. To date, very few studies have been conducted on pressure injury in spinal surgery; additionally, analysis of the risk factors associated with pressure injury have shown inconclusive results.

Moreover, previous studies have mostly included the injury found immediately after surgery as well as the injuries that were discovered during the postoperative period of 24 h to several months. To minimize the postoperative effect and analyze only the intraoperative factors, it is necessary to limit the study to injuries found immediately after surgery.

The relatively high incidence of pressure injury reported so far indicates that risk assessment and the use of protective measures should be improved [7]. Additionally, the literature shows that approximately 95% of all pressure injuries in perioperative patients can be prevented with early risk assessment and appropriate interventions [8]. Therefore, it is important to particularly target reversible factors through prior risk assessment for the patient group with a high risk of pressure injury. This study aimed to identify the incidence of perioperative pressure injury during spinal surgery and explore the perioperative risk factors that may potentially contribute to pressure injury.

**MATERIALS AND METHODS**

This study analyzed the data of 692 patients who underwent spinal surgery from March 2016 to May 2018 at a single university teaching hospital. Ethical approval from the Institutional Review Board (IRB no. 2019-08-004) was received. Data were retrospectively analyzed from the database of the institution’s electronic medical records (EMR).

There were 20 duplicate cases in the initial data preparation stage, which were duplicated due to reoperation two (18 patients) and three times (1 patient) in the same patient, and repeat surgery by the same person may introduce a bias against the risk of pressure injury. In all cases, only the first spinal surgery was included in the analysis.

Patients aged 18 years and older, of both sexes, undergoing elective or emergency spinal surgeries were included in the study. We excluded 9 cases of cervical spine operation, supine/lateral position, simple short procedures such as ‘wound debridement’ or ‘incision & drain.’ Ultimately, 663 patients were included in the study (Fig. 1).

**Outcome and risk factor evaluation**

The primary outcome was the occurrence of pressure injury. Attending anesthesiologists, surgeons, and scrub nurses examined the patient’s whole body before and after the surgery. The injury site, size, and characteristics of the pressure injury were obtained from the description in the EMR. We categorized the pressure injuries into 4 stages according to the NPUAP classification system [1].

Potential risk factors for pressure injury were selected based on previous studies and expert opinions. The authors first considered the common and known risk factors, obtained from previous studies of risk assessment for pressure injury [2,3,9–11]. These commonly known risk factors...
can be classified into three categories: preoperative, intraoperative, and postoperative factors. We focused on the preoperative and intraoperative factors that might be mediated by an anesthesiologist to prevent pressure injury.

We explored the following characteristics as preoperative risk factors for pressure injury: demographic data (age, sex, body mass index), current status regarding smoking/alcohol consumption, history or presence of various comorbidities (cardiovascular, respiratory, renal, hepatic, diabetes, malignancy, and neurologic disease), preoperative laboratory test results (hemoglobin, hematocrit, protein, albumin, glucose, blood urea nitrogen, creatinine, sodium, potassium, etc.), and American Society of Anesthesiologists classification.

Additionally, intraoperative risk factors consisted of anesthesia duration, total amount of intraoperative fluid administration, total amount of all intraoperative blood product transfusion, total amount of intraoperative bleeding, average body temperature during surgery, and the total dose of vasopressor agent administered. These risk factors were selected based on consensus among experts and surgeons on the likelihood of these factors affecting the development of a pressure injury [10].

**Statistical analysis**

All statistical analyses were performed using R software (version 3.6.1, R Foundation for Statistical Computing, Austria; https://www.R-project.org/). We compared the clinical characteristics between the pressure injury group and the non-injury group using a Student’s *t*-test or Mann–Whitney *U* test for continuous variables based on the results of a Shapiro-Wilk normality test, and we used a Fisher’s exact test or chi-square test for categorical or proportional variables.

A multivariable logistic regression analysis based on a binomial generalized linear model was performed to identify the risk factors associated with perioperative pressure injury. We explored the relationship between each variable and the pressure injury through a univariate logistic regression analysis, and then performed multivariable logistic regression, which consisted of variables with *P* < 0.1 from the univariate logistic regression. Independent risk factors with *P* < 0.05 in the multivariable analysis were considered statistically significant. To produce the final logistic regression model, the risk factors were selected by weighting their clinical implications and statistical values (e.g., Akaike

---

**Fig. 1.** CONSORT flow diagram of study. CONSORT: consolidated standards of reporting trials.
Information Criterion). Hosmer–Lemeshow goodness-of-fit tests were used to assess the fitness of the logistic regression model. The optimal cut-off point of the explored risk factor was determined by maximizing the sum of sensitivity and specificity using a receiver operating characteristic (ROC) curve to measure association and evaluate the prediction accuracy of a significant risk factor for the occurrence of pressure injury.

RESULTS

All results are expressed as mean ± standard deviation or median (interquartile range; 1Q, 3Q) as appropriate. The incidence of all stages of pressure injury was 5.9% (39/663). All patients had a relatively low stage of pressure injury; nine patients (18%) had stage-1 and 40 patients (82%) had stage-2 injuries, while none had a stage-3 injury or higher. Eight patients had two different sites of injuries, and one patient had three different sites of injuries. The face and inguinal regions were the most injured sites (both 28.6%). Other sites, in order of frequency of injury occurrence, included the following: chest (24.5%), anterior superior iliac spine (6.1%), abdomen (6.1%), arm (4.1%), and femur (2.1%) (Table 1).

Table 2 shows a comparison of the general characteristics of patients from the pressure injury and non-pressure injury groups. These characteristics include factors that could potentially be considered as risk factors for pressure injury, general physiological information of the patient, and the characteristics related to the patient’s surgical outcome, such as total duration of hospital stay.

The pressure injury group showed a 13% longer hospitalization period and a 3% lower protein plasma concentration than the non-pressure injury group. There were a total of 3 (7.7%) cases of malignancy in the pressure injury group, which included solid tumors in organs such as the prostate, uterus, and lung. They also had 25% longer surgery time and larger volumes of fluid and blood product than the other group. Intraoperative bleeding was also 20% higher than that of the non-pressure injury group (Table 2).

Table 3 presents the results of the univariate and baseline/final multivariable logistic regression analyses for the perioperative risk factors of pressure injury. All previously known and clinically estimated risk factor candidates were explored using univariate analyses. Through univariate analysis, the following seven independent variables with a cut-off value of $P < 0.1$ were included in the multivariate analysis: preoperative plasma concentration of protein, surgery time, total infused volume of fluids, total administered volume of blood product, total volume of intraoperative bleeding, total administered amounts of vasopressor, and comorbidity of malignancy. The final reduced model indicated that a preoperative plasma concentration of protein was associated with a 0.5-fold lower pressure injury (adjusted odds ratio: 0.502; 95% confidence interval, 0.267–0.953; $P = 0.034$) (Table 3).

The Hosmer-Lemeshow goodness-of-fit test showed that the fitted values of the multivariable logistic regression model (final reduced model) showed chi-squared = 9.3867, df = 8, and $P$ value = 0.311 and, therefore, was a valid model. All variables in our final reduced regression model had a variance inflation factor value below 10, which showed no collinearity. In the ROC analysis, the final reduced model showed an area under the curve of 0.711 in pressure injury, with an optimal cut-off value of 5.17, and 68.6% sensitivity and 65.2% specificity.

DISCUSSION

The incidence of pressure injury in this study was approxi-
### Table 2. Basic Characteristics of Patients with/without Pressure Injury

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-pressure injury (n = 624)</th>
<th>Pressure injury (n = 39)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>65.0 (55.0, 73.5)</td>
<td>67.0 (55.5, 74.0)</td>
<td>0.741</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>257/367</td>
<td>16/23</td>
<td>1</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.0 (21.8, 26.4)</td>
<td>17.0 (15.0, 32.5)</td>
<td>0.017</td>
</tr>
<tr>
<td>Smoking</td>
<td>109 (17.5)</td>
<td>6 (15.4)</td>
<td>0.908</td>
</tr>
<tr>
<td>Alcohol drinking</td>
<td>190 (30.4)</td>
<td>10 (25.6)</td>
<td>0.649</td>
</tr>
<tr>
<td>Hospitalization period</td>
<td>15.0 (13.0, 20.0)</td>
<td>17.0 (15.0, 32.5)</td>
<td>0.017</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>148 (23.7)</td>
<td>9 (23.1)</td>
<td>1</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>315 (50.5)</td>
<td>22 (56.4)</td>
<td>0.580</td>
</tr>
<tr>
<td>Respiratory</td>
<td>22 (3.5)</td>
<td>2 (5.1)</td>
<td>0.938</td>
</tr>
<tr>
<td>Hepatic</td>
<td>31 (5.0)</td>
<td>3 (7.7)</td>
<td>0.708</td>
</tr>
<tr>
<td>Renal</td>
<td>16 (2.6)</td>
<td>0 (0)</td>
<td>0.635</td>
</tr>
<tr>
<td>Neurologic</td>
<td>33 (5.3)</td>
<td>1 (2.6)</td>
<td>0.708</td>
</tr>
<tr>
<td>Malignancy</td>
<td>15 (2.4)</td>
<td>3 (7.7)</td>
<td>0.143</td>
</tr>
<tr>
<td>ASA class</td>
<td>6 (1.0)</td>
<td>0 (0.0)</td>
<td>0.214</td>
</tr>
<tr>
<td>Class 1</td>
<td>439 (72.0)</td>
<td>27 (71.1)</td>
<td></td>
</tr>
<tr>
<td>Class 2</td>
<td>163 (26.7)</td>
<td>10 (26.3)</td>
<td></td>
</tr>
<tr>
<td>Class 3</td>
<td>2 (0.3)</td>
<td>1 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Class 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Preoperative test</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>12.6 (116, 13.9)</td>
<td>12.4 (11.6, 13.5)</td>
<td>0.771</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>40.0 (36.8, 43.1)</td>
<td>39.1 (37.1, 41.6)</td>
<td>0.559</td>
</tr>
<tr>
<td>WBC (10^3)/µl</td>
<td>6.9 (5.8, 8.5)</td>
<td>7.3 (5.9, 9.7)</td>
<td>0.378</td>
</tr>
<tr>
<td>Platelet (10^3)/µl</td>
<td>239.0 (200.0, 288.0)</td>
<td>258.5 (198.5, 295.0)</td>
<td>0.517</td>
</tr>
<tr>
<td>PT INR</td>
<td>1.0 (0.9, 1.0)</td>
<td>1.0 (0.9, 1.0)</td>
<td>0.516</td>
</tr>
<tr>
<td>AST (IU)</td>
<td>25.0 (21.0, 33.0)</td>
<td>25.0 (21.0, 28.5)</td>
<td>0.754</td>
</tr>
<tr>
<td>ALT (IU)</td>
<td>19.0 (13.0, 28.0)</td>
<td>20.0 (15.5, 25.0)</td>
<td>0.351</td>
</tr>
<tr>
<td>Plasma concentration of protein (g/dl)</td>
<td>7.3 (6.9, 7.6)</td>
<td>7.1 (6.8, 7.3)</td>
<td>0.042</td>
</tr>
<tr>
<td>Plasma concentration of albumin (g/dl)</td>
<td>4.2 (4.0, 4.5)</td>
<td>4.1 (4.0, 4.4)</td>
<td>0.132</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>116.0 (101.0, 139.0)</td>
<td>126.0 (114.5, 147.0)</td>
<td>0.019</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>15.6 (12.5, 20.3)</td>
<td>17.7 (13.6, 21.1)</td>
<td>0.209</td>
</tr>
<tr>
<td>Cr (mg/dl)</td>
<td>0.7 (0.6, 0.9)</td>
<td>0.7 (0.6, 0.9)</td>
<td>0.459</td>
</tr>
<tr>
<td>Na⁺ (mEq/L)</td>
<td>138.0 (136.0, 139.0)</td>
<td>138.0 (136.5, 139.0)</td>
<td>0.301</td>
</tr>
<tr>
<td>K⁺ (mEq/L)</td>
<td>4.0 (3.8, 4.2)</td>
<td>4.0 (3.8, 4.3)</td>
<td>0.742</td>
</tr>
<tr>
<td>Cl⁻ (mEq/L)</td>
<td>105.0 (103.0, 106.0)</td>
<td>105.0 (102.0, 106.0)</td>
<td>0.622</td>
</tr>
<tr>
<td><strong>Intraoperative factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anesthesia time (h)</td>
<td>3.9 (3.0, 5.0)</td>
<td>4.8 (3.8, 5.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Surgical operation time duration (h)</td>
<td>2.8 (2.0, 3.8)</td>
<td>3.5 (2.8, 4.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Total infused volume of fluids (L)</td>
<td>2.0 (1.4, 2.6)</td>
<td>2.7 (1.9, 3.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total administered volume of blood product (L)</td>
<td>0.0 (0.0, 0.2)</td>
<td>0.1 (0.0, 0.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>Total volume of intraoperative bleeding (L)</td>
<td>0.5 (0.2, 0.7)</td>
<td>0.6 (0.5, 1.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Average body temperature (°C)</td>
<td>36.1 (35.9, 36.3)</td>
<td>36.1 (35.9, 36.3)</td>
<td>0.774</td>
</tr>
<tr>
<td>Total administered amounts of vasopressor (mg)</td>
<td>50.0 (0.0, 200.0)</td>
<td>75.0 (0.0, 225.0)</td>
<td>0.425</td>
</tr>
</tbody>
</table>

Values are expressed as median (1Q, 3Q), number of patients (%), ASA: American Society of Anesthesiologists, WBC: white blood cell count, PT INR: prothrombin time international normalized ratio, AST: aspartate aminotransferase, ALT: alanine aminotransferase, BUN: blood urea nitrogen, Cr: creatinine.
Proteins are generally known as indicators of a patient’s nutritional status and play an important role in healing damaged skin by affecting collagen synthesis, activation of the immune system, and fibroblast proliferation [16]. Among all plasma proteins, albumin has the largest proportion. Previous studies often used albumin levels instead of proteins to demonstrate a correlation between pressure injury and serum protein levels [2,5]. However, the results are unclear [2,3,5,14,17]. Albumin has a short half-life; thus, it may not reflect the patient’s nutritional status at the time of surgery. Various proteins, such as α-, β-, and γ-glob-
ulin and fibrinogen exist in plasma, and the colloid oncotic pressure (COP) is determined by the total amount of proteins present in plasma. When a specific protein in the plasma decreases, COP may also decrease, resulting in interstitial edema, which is a major cause of pressure injury [10].

Choi et al. [3] reported that the risk increased 4.5 times in surgeries with a duration greater than 4 h, and Hicks [18] reported twice the incidence in surgeries that lasted longer than 4 h. In this study, the average surgery time was 3.5 h, which may have contributed to the low association between this factor and pressure injury occurrence. Large intraoperative bleeding can cause both hypotension and low hemoglobin levels, which may decrease tissue perfusion and oxygenation. Consequently, it may increase the risk of pressure injury. In this study as well as previous studies, the intraoperative total amount of fluid and blood products, the total volume of bleeding, and the total amount of vasopressor, showed a positive correlation with pressure injury occurrence (Table 3) [3,11,19]. Nutritional deficits, such as cachexia and low activity levels due to fatigue, are usually accompanied by malignancy [20]. These factors are highly related to the previously known risk factors of pressure ulcers, and Ranzani et al. showed its correlation [21]. However, although some patients have completed chemotherapy and radiation therapy and are in a complete remission state, it is still difficult to explain why pressure injury occurred in these patients.

Pressure injury can cause prolonged hospitalization. Han et al. [22] reported that pressure injuries influenced mortality (OR 2.18) and increased the risk of increased hospital stay (OR 5.55), along with increased risk of readmission (OR 1.30) and emergency department visits after discharge (OR 1.70). Analysis of the association between pressure injury and medical costs requires further research using substantial data.

There are a few limitations to this study. Since this is a study performed with patients from a single institution with a relatively small number of patients, differences in surgery time, operating tables, protective equipment, and comorbidities of patient groups may have affected the results. There may have been other potential confounders. The area under the curve value of 0.711 may indicate that the model used was not optimal. Therefore, our model may not fully explain the risk factors for intraoperative pressure injury, and it is expected that there are more potential risk factors that we were unable to identify.

In conclusion, the incidence of pressure injury was considerable and mainly lower-stage injuries occurred. Pressure injury mainly occurred in the region directly receiving weight load during spinal surgery. In the cases of pressure injuries occurred within a relatively short period of time as like as intraoperative period, preoperative risk factors such as plasma protein level rather than intraoperative factors may be more closely related to the pressure injury. Although further follow-up studies are needed to prove this assumption, it is believed that the patient’s nutritional status and fluid status related to colloid oncotic pressure have a substantial influence on the incidence of pressure injury [10,16]. Therefore, proper correction of plasma protein level before surgery is very important in preventing pressure injuries.

ACKNOWLEDGEMENTS

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Letter to the Editor

Change of inspired oxygen concentration and temperature in low flow anesthesia

TO THE EDITOR: For low-flow anesthesia, the anesthesia workstation, monitoring technology and desflurane, sevoflurane, which were a low blood-gas partition coefficient, have gradually been adopted. Low-flow anesthesia is considered effective in maintaining the heat and the moisture of the breathing circuit and preserving the mucociliary function of the respiratory tract. In addition, it is safer and more effective at lowering the economic burden and global warming potential [1,2]. We read, with interest, your paper on “Change of inspired oxygen concentration in low flow anesthesia” (Anesth Pain Med 2020; 15: 434-40). We appreciate your results and have some questions to discuss.

We have a few questions about the monitoring and the maintenance of body temperature. How did you maintain and monitor the temperature of the operating room? Was the patient’s temperature measured only in the esophagus? What was the depth of the esophageal temperature probe? Depending on the room temperature and the depth of insertion, the body temperature can change with ambient influences, such as blood flow of venous return and inhaled gas temperature [3]. Therefore, the authors used a heated breathing system and a heat moisture exchanger (HME) to heat the breathing circuit. During anesthetic care, the patient’s temperature did not show a statistically significant change after 60–75 min of low flow. However, it started increasing significantly after 120 min of low flow.

In this study, soda lime (CO₂ absorber) and a standard circular rebreathing circuit with a heated breathing circuit were used. Did you use the HME in the heated breathing circuit? One CO₂ molecule, exhaled by the patient, produces two water (H₂O) molecules and generates approximately 40°C of heat during its reaction with soda lime. The moisture and heat generated by the reaction are sufficient for the patient’s humidification and warmth during anesthesia 30 min after induction [1,4]. Therefore, if a low-flow system is used, there is no reason to use a heated breathing circuit and HME, sufficient heat and moisture can be maintained without a heated breathing circuit and HME [1–5]. We think that the increased temperature within the circuit is not an advantage but a problem caused by adding the heated breathing circuit and HME during low flow rather than high flow. What do you expect to get if you do not attach either of or both the heating breathing circuit and HME?

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REFERENCES
IN REPLY: We would like to thank the letter for their positive comments on our paper. The response to the letter gave us the opportunity to supplement methodology of the paper. We agree with the author of the letter that use of a heated circuit or heat moisture exchanger (HME) for low-flow anesthesia is not required. In low flow anesthesia, the heating and humidification effect of the anesthesia circuit is well known. Humidifying and warming effect of low flow anesthesia has been reported to be sufficient to replace the effect of HME and heating circuits at high flow anesthesia [1]. We focused on oxygen concentration during low and high flow anesthesia, therefore we used the same heating circuit and HME in both groups for variable control.

In our hospital, the ambient temperature of the operating room was maintained at 20–23°C [2]. The patients in this study were anesthetized under these room temperature conditions. If the patient’s body temperature is not stable, it is natural to control the room temperature outside the range, and this did not happen in the study.

Esophageal temperature was not measured for all patients, but either the axillary or esophageal temperature may be measured depending on the situation. In this study, only the esophageal temperature was measured to minimize the deviation due to the measurement method. The esophageal temperature sensor used in this study was an Esophageal Stethoscope with Temperature Sensor 18 French (DeRoyal, USA). The temperature sensor is mounted at the depth where heart sounds are best heard using a stethoscope.

We focused on oxygen concentration during low and high flow anesthesia. Therefore, we studied patients undergoing thyroidectomy. Since temperature management was not challenging for these patients, this study could not examine the detailed effects of low-flow anesthesia on temperature management. Further research may be needed to clarify this aspect.

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REFERENCES
1. Online manuscript review process and guidelines for submission

1) All manuscripts must be submitted through the online submission system (available at http://submit.anesth-pain-med.org). Any inquiries about the manuscripts should be posted on the “Contacting Author” page, which is available to the right upon logging in. Specify the manuscript number, author, and corresponding author when posting an inquiry.

2) The corresponding author should be a faculty. The corresponding author will be notified by e-mail whenever there is any change in the status of a submitted manuscript, and any resubmission can only be made by the corresponding author.

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2. Mandatory English editing for Korean authors

APM has made English editing mandatory for manuscripts submitted on or after September 1, 2013. Authors are responsible for the cost of editing. For English manuscripts, please submit them to a professional editing service after acceptance and upload the edited file and certificate of editing in the manuscript submission system. Manuscripts edited by an individual and not through a professional editing service will not be accepted. Manuscripts submitted in Korean will be translated into English by the Society after acceptance, and Korean version will be published only on the website (www.anesth-pain-med.org).
Anesthesia and Pain Medicine (APM) is the official scientific journal of Korean Society of Neuroscience in Anesthesiology and Critical Care (KSNACC), The Korean Society for Anesthetic Pharmacology (KSAP), The Korean Society of Obstetric Anesthesiologists (KSOA), The Korean Society of Pediatric Anesthesiologists (KSPA), Korean Neuromuscular Research Society (KNRS), Korean Society of Cardiothoracic and Vascular Anesthesiologists (KSCVA), Korean Society of Transplantation Anesthesiologists (KSTA), and The Korean Spinal Pain Society (KSPS) and Korean Society of Regional Anesthesia (KSSA), and Korean Society for Airway Management (KSNAM). The abbreviated title is "Anesth Pain Med". It is published four times a year on the last day of January, April, July, and October in English.

I. Editorial Policy

The Editor assumes that all authors listed in a manuscript have agreed with the following policy of the APM on submission of manuscript. Except for the negotiated secondary publication, manuscript submitted to the APM must be previously unpublished and not be under consideration for publication elsewhere. Under any circumstances, the identities of the referees will not be revealed. Minimum publication charges and additional fee for reprints will due on every manuscript. All published manuscripts become the permanent property of the Korean Society of Anesthesiologists (KSA) and may not be published elsewhere without written permission. APM adheres completely to guidelines and best practices published by professional organizations, including Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (http://www.icmje.org/icmje-recommendations.pdf) from ICMJE and Principles of Transparency and Best Practice in Scholarly Publishing (joint statement by COPE, DOAJ, WAME, and OASPA; http://doaj.org/bestpractice) if otherwise not described below.

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APM focuses on clinical research, experimental research, case reports, reviews, and letters to the editor, online images and various introductions.

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APM publishes articles in English. Manuscript submitted in Korean will be translated into English by the society after acceptance, Korean version will be published only on the website (www.anesth-pain-med.org).

Spellings should abide by American spellings. Medical terminology should be written based on the most recent edition of Dorland’s Illustrated Medical Dictionary. Accepted manuscripts are requested to be proofread by professional English editors.

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In addition to members of the Korean Society of Anesthesiologists, any researcher throughout the world can submit a manuscript if the scope of the manuscript is appropriate. Authors are requested to submit their papers electronically by using the online manuscript submission system, available at: http://submit.anesth-pain-med.org. Authors, reviewers, and editors send and receive all correspondences through this system. Final revisions by authors should be submitted within 1 week of the request.

4. Data Availability Statement

Data sharing is encouraged by the APM, but a Data Availability Statement will be required and published with the manuscript. Authors will be provided the following options during submission or may use draft their own.

- The datasets generated during and/or analyzed during the current study are available in the [NAME] repository, [PER-SISTENT WEB LINK TO DATASETS]
- The datasets generated during and/or analyzed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.
- The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.
• Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.
• All data generated or analyzed during this study are included in this published article [and its supplementary information files].
• The data that support the findings of this study are available from [third party name] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [third party name].

5. Peer review process

APM uses double-blind review, which means that both the reviewer and author identities are concealed from the reviewers, and vice versa, throughout the review process. To facilitate this, authors need to ensure that their manuscripts are prepared in a way that does not give away their identity. If one or more of editors are involved as authors, the editor(s) should not be involved in the peer reviewer selection, evaluation, or decision process. Submitted manuscripts will be reviewed by 2 or more experts in the corresponding field. The Editorial Board may request authors to revise the manuscripts according to the reviewer’s opinion. After revising the manuscript, the author should upload the revised files with a reply to each item of the reviewer’s opinion. Additions and amendments to the revised manuscript should be highlighted in red. The author’s revisions should be completed within 60 days after the request. If it is not received by the due date, the Editorial Board will not consider it for publication. To extend the revision period to more than 60 days, the author should negotiate with the Editorial Board. The manuscript review process should be finished the second review. If the reviewers wish further review, the Editorial Board may consider it. The Editorial Board will make a final decision on the approval for publication of the submitted manuscripts and can request any further corrections, revisions, and deletions of the article text if necessary. Statistical editing is also performed if the data need professional statistical review by a statistician. The review and publication processes that are not described in the Instructions for Authors will be incorporated into the Editorial Policy Statements approved by the Council of Science Editors Board of Directors, available at: www.councilscienceeditors.org/.

6. Article processing charge and publication fee

There is no submission-related fee. Article processing charge (APC) of KRW 300,000 (USD 250) per article will be issued to the corresponding author. APC is waived if the affiliations of the first and corresponding authors are outside Korea. APC for invited articles is also waived.

7. Copyrights and secondary publication

Copyrights of all published materials are owned by the APM. On behalf of co-author(s), corresponding author must complete and submit the journal’s copyright transfer agreement, which includes a section on the disclosure of potential conflicts of interest based on the recommendations of the International Committee of Medical Journal Editors, “Uniform Requirements for Manuscripts Submitted to Biomedical Journals.” A copy of the form is made available to the submitting author within the online manuscript submission process. It is possible to republish manuscripts if ONLY the manuscripts satisfy the condition of secondary publication of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, available at: http://www.icmje.org

8. Open access

APM is an Open Access journal accessible for free on the Internet. Accepted peer-reviewed articles are freely available on the journal website for any user, worldwide, immediately upon publication without additional charge.

III. Research and Publication Ethics Guidelines

For the policies on research and publication ethics, the “Good Publication Practice Guidelines for Medical Journals” (https://www.kamje.or.kr/board/view?b_name=bo_publication&bo_id=13) or the “Ethical Guidelines on Good Publication” (http://publicationethics.org/resources/guidelines) or “Ethical Considerations in the International Committee of Medical Journal Editors” (http://www.icmje.org/recommendations) are applied.

1. Conflict-of-interest statement

The corresponding author is required to summarize all authors’ conflict of interest disclosures. Disclosure form shall be same with ICMJE Uniform Disclosure Form for Potential Conflicts of Interest (www.icmje.org/conflicts-of-interest). A conflict of interest may exist when an author (or the author’s institution or employer) has financial or personal relationships or affiliations that could influence (or bias) the author’s decisions, work, or manuscript. All authors should disclose their conflicts of in-
terest, i.e., (1) financial relationships (such as employment, consultancies, stock ownership, honoraria, earned paid expert testimony), (2) personal relationships, (3) academic competition, and (4) intellectual passion. These conflicts of interest must be included as a footnote on the title page or in the Acknowledgements section.

All sources of funding should be declared on the title page or in the Acknowledgements section at the end of the text. If an author's disclosure of potential conflicts of interest is determined to be inaccurate or incomplete after publication, a correction will be published to rectify the original published disclosure statement, and additional action may be taken as necessary.

If one or more of editors are involved as authors, the authors should declare conflict of interests.

Ex) AAA has been an editor of the Anesthesia and Pain Medicine since 2017; however, he was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

2. Statement of informed consent

Copies of written informed consents and Institutional Review Board (IRB) approval for clinical research are recommended kept. The editor or reviewers may request copies of these documents to make potential ethical issues clear.

3. Protection of privacy, confidentiality, and written informed consent

Identifying details should not be published in written descriptions, photographs, or pedigrees unless it is essential for scientific purposes and the patient (or his/her parents or guardian) provides written informed consent for publication. Additionally, informed consent should be obtained in the event that anonymity of the patient is not assured. For example, masking the eye region of patients in photographs is not adequate to ensure anonymity. If identifying characteristics are changed to protect anonymity, authors should provide assurance that alterations do not distort scientific meaning. When informed consent has been obtained, this should be indicated in the published article.

4. Protection of human and animal rights

In the reporting of experiments that involve human subjects, it should be stated that the study was performed according to the Helsinki Declaration of 1975 (revised 2013) (Available from https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) and approved by the Institutional Review Board (IRB) of the institution where the experiment was performed. Clinical studies that do not meet the Helsinki Declaration will not be considered for publication. Identifying details should not be published (such as name, initial of name, ID numbers, or date of birth).

In the case of an animal study, a statement should be provided indicating that the experimental processes, such as the breeding and the use of laboratory animals, were approved by the Research Ethics Committee (REC) of the institution where the experiment was performed or that they did not violate the rules of the REC of the institution or the NIH Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council, https://www.nap.edu/catalog/5140/guide-for-the-care-and-use-of-laboratory-animals). The authors should preserve raw experimental study data for at least 1 year after the publication of the paper and should present this data if required by the Editorial Board.

5. Registration of the clinical research

It is recommended that all clinical trials be registered in the primary registry before submission. APM accepts registration in any of the primary registries that participate in the World Health Organization (WHO) International Clinical Trials Portal (http://www.who.int/ictrp/en), NIH ClinicalTrials.gov (http://www.clinicaltrials.gov), or Korea Clinical Research Information Service (CRiS, http://cris.nih.go.kr).

6. Reporting guidelines

The APM recommends a submitted manuscript to follow reporting guidelines appropriate for various study types. Good sources for reporting guidelines are the EQUATOR Network (www.equatornetwork.org) and the NLM's Research Reporting Guidelines and Initiatives (www.nlm.nih.gov/services/research_report_guide.html).

7. Author and authorship

An author is considered as an individual who has made substantive intellectual contributions to a published study and whose authorship continues to have important academic, social, and financial implications.

Authorship credit should be based on: (1) substantial contributions to the conception or design of the work, or to the acquisition, analysis, or interpretation of data for the work; (2) the
drafting of the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement on taking accountability for the accuracy or integrity of the work. Authors should meet these four criteria. These criteria distinguish the authors from other contributors.

When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. When submitting a manuscript authored by a group, the corresponding author should clearly indicate the preferred citation and identify all individual authors as well as the group name. Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship. Journals generally list other members of the group in the Acknowledgments section.

8. Plagiarism and duplicate publication

Plagiarism is the use of previously published material without attribution. Prior to peer review, all manuscripts are screened for plagiarism by the Editor-in-Chief using iThenticate. When plagiarism is detected at any time before publication, the APM editorial office will take appropriate action as directed by the standards set forth by the Committee on Publication Ethics (COPE). For additional information, please visit http://www.publicationethics.org. Text copied from previously published work is interpreted using the following taxonomy:

1) Intellectual theft
   Deliberate copying of large blocks of text without attribution
2) Intellectual sloth
   Copying of “generic” text, e.g., a description of a standard technique, without clear attribution
3) Plagiarism for scientific English
   Copying of verbatim text, often from multiple sources
4) Technical plagiarism
   Use of verbatim text without identifying it as a direct quotation but citing the source
5) Self-“plagiarism”

Manuscripts are only accepted for publication if they have not been published elsewhere. Manuscripts published in this journal should not be submitted for publication elsewhere. Duplicate submissions identified during peer review will be immediately rejected. Duplicate submissions that are discovered after publication will be retracted. It is mandatory for all authors to resolve any copyright issues when citing a figure or table from a different journal that is not open access.

When duplicate publication is detected, the APM editorial office will notify the counterpart journal on this violation. Additionally, it will be notified to the authors’ affiliation and penalties will be imposed on the authors. It is possible to republish manuscripts if the manuscripts satisfy the condition of secondary publication of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, available at: www.icmje.org. If the author or authors wish to obtain a duplicate or secondary publication for reasons such as publication for readers of a different language, the author(s) should obtain approval from the Editors-in-Chief of both the first and second journal.

IV. Manuscript Preparation

APM recommends compliance with some or all of the following guidelines (www.equatornetwork.org/library).

- CONSORT for reporting of randomized controlled trials (http://www.consort-statement.org)
- STARD for reporting of diagnostic accuracy studies (http://www.stard-statement.org)
- STROBE for reporting of observational studies in epidemiology (http://www.strobe-statement.org)
- PRISMA for reporting of systematic reviews (http://www.prisma-statement.org)
- MOOSE for reporting of observational studies (http://www.emgo.nl/kc/reporting-your-study-results-in-a-scientific-article)
- GLOBAL ADVANCES in Health and Medicine for reporting of clinical cases (http://www.gahmj.com)

1. Word processors and format of manuscripts

A manuscript must be written in proper and clear English or Korean. Our preferred file format is DOCX or DOC. Manuscripts should be typed double-spaced on A4-sized paper, using 12 point font in English, using 10 point font in Korean.

2. Abbreviation of terminology

Abbreviations should be avoided as much as possible. When they are used, full expression of the abbreviated words should be provided at the first use, with the abbreviation following in parentheses.

Ex) target controlled infusion (TCI)

After that, “TCI” can be used instead of “target controlled infusion.” Common abbreviations may be used, however, such as DNA. Abbreviations can be used if they are listed as a MeSH subject heading (https://www.ncbi.nlm.nih.gov/mesh).
3. Word spacing

1) Leave 1 space on each side when using arithmetic marks such as +, −, ×, etc.
   Ex) 24 ± 2.5
   Leave no space when using hyphen between words.
   Ex) intra-operative
2) When using parentheses, leave 1 space on each side in English, and leave no space in the Korean manuscript.
3) When using brackets in parentheses, apply square brackets.
   Ex) ([ ])
4) Manuscripts in Korean should obey the rules of Korean spelling (www.korean.go.kr).

4. Citations

1) If a citation has 2 authors, write as “Hirota and Lambert”. If there are more than 3 authors, apply “et al.” at the end of the first author’s surname.
   Ex) Kim et al. [1]
2) Citations should be applied after the last word.
   Ex) It is said that hypertension can be induced [1] and the way to injure the brain [2] is...
   Ex) Choi and Kim [1] reported...
3) Apply citations before a comma or period.
   Ex) ...is reported [1],
4) Several or coupled superscripts can be written as [1–5] or [1,3,5].

5. Arrangement of manuscript

The manuscript should be organized in the order of title, abstract, introduction, materials and methods, results, discussion, acknowledgments, references, tables, figures, and figure legends. Figures should be uploaded as separate files. The title of each new section should begin on a new page. The conclusion should be included in the discussion section. Number pages consecutively, beginning with the first page of the manuscript. Page numbers should be placed at the middle of the bottom of the page. For survey-based clinical studies, the original survey document does not need to be included in the body of the manuscript but may be included as a supplement in an appendix.

6. Organization of manuscript

1) Clinical or experimental research
   (1) Cover page (upload separately)
      ① Title
      Title should be concise and precise. The first word should be capitalized. Drug names in the title should be written with generic names, not brand names. For the title, only the first letter of the first word should be capitalized.
      Ex) Effect of smoking on bronchial mucus transport velocity under total intravenous anesthesia ···········
      Ex) Effect of Smoking on Bronchial Mucus Transport Velocity under Total Intravenous Anesthesia ···········
      Provide drug names as generic names, not product names.
      Ex) In CPR, Isosorbide Dinitrate is, ···········
      Ex) In CPR, Isosorbide Dinitrate (Isoket®) is, ···········
      Ex) In CPR, Isoket® is, ···········
   ② Abstract
      All manuscripts should contain a structured abstract that is written only in English. Authors should pro-
vide an abstract of no more than 250 words. It should contain 4 subsections: Background, Methods, Results, and Conclusions. Citation of references is not permitted in the abstract. A list of keywords at least 4, with a maximum of 10 items, should be included at the end of the abstract. Key words should be selected from MeSH (https://www.ncbi.nlm.nih.gov/mesh), and these should be written in small letters with the first letter capitalized. Separate each word with a semicolon (;), and include a period (.) at the end of the last word. Ex) Keywords: Carbon dioxide; Cerebral vessels; Oxygen; Spinal analgesia.

Introduction
The introduction should address the purpose of the article concisely and include background information that is relevant to the purpose of the paper.

Materials and Methods
The materials and methods section should include sufficient details regarding the design, subjects, and methods of the research in order, as well as methods used for data analysis and control of bias in the study. Sufficient details must be provided in the methodology section of an experimental study so that it can be further replicated by others.

Institute and author names should be avoided. When reporting experiments with human or animal subjects, the authors should indicate whether they received approval from the Institutional Review Board for the study. When reporting experiments with animal subjects, the authors should indicate whether the handling of the animals was supervised by the Institutional Board for the Care and Use of Laboratory Animals. Demographic data should be included in the materials and methods section if applicable. As a rule, subsection titles are not recommended. If several study designs were used, then subtitles can be used without assigning numbers.

Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity and justify their relevance.

Units Laboratory information should be reported using the International System of Units [SI], available at: https://www.nist.gov/pml/special-publication-811

<Exceptions>
A. The unit for volume is "L," while others should be written as "dl, ml, μl".
Ex) 1 L, 5 ml
B. The units for pressure are mmHg or cmH₂O instead of Pascal.
C. Use Celsius for temperature. °C
D. Units for concentration are M, mM, μM.
Ex) μmol/L; [ × ]
E. When more than 2 items are presented, diagonal slashes are acceptable for simple units. Negative exponents should not be used.
Ex) mg/kg/min [O], mg · kg⁻¹ · min⁻¹ [×]

F. Leave 1 space between number and units, except %, °C.
Ex) 5 mmHg
Ex) 5%, 36°C

G. Units of time
Ex) hour: 1 h = 60 min = 3,600 s, day: 1 d = 24 h = 86,400 s

• Machines and equipment
Provide model name and manufacturer’s name, and country. Do not put “.” between words when writing the names of countries.
Ex) U.S.A. [×], USA [O]

For drug names, use generic names. If a brand name should be used, insert it in parentheses after the generic name. Provide® or ™ as a superscript and the manufacturer’s name and country.

• Ions
Ex) Na⁺[O], Mg²⁺[O], Mg²⁺[×], Mg²⁺[×]
Ex) Premedicated magnesium [O]
Ex) Premedicated Mg²⁺ [O]

Results
Results should be presented in a logical sequence in the text, tables, and figures, giving the main or most important findings first. Do not repeat all of the data provided in the tables or figures in the text; emphasize or summarize only the most important observations. Results can be sectioned by subsection titles but should not be numbered. Citation of tables and figures should be provided as Table 1 and Fig. 1.

Type or print each table on a separate page. Figures should be uploaded as separate tif, jpg, pdf, gif, ppt files.
6 Statistics

Precisely describe the methods of statistical analysis and computer programs used. Mean and standard deviation should be described as mean ± SD, and mean and standard error should be written as mean ± SEM. Median and interquartile should be described as median (IQR, 3Q). When displaying P values, use a capital P and do not put a “.” between “P” and “value”.

A. Describe the statistical tests employed in the study with enough detail so that readers can reproduce the same results if the original data are available. The name and version of the statistical package should be provided.

B. Authors should describe the objective of the study and hypothesis appropriately. The primary/secondary endpoints are predetermined sensibly according to the objective of the study.

C. The characteristics of measured variables should determine the use of a parametric or nonparametric statistical method. When a parametric method is used, the authors should describe whether the basic statistical assumptions are met. For an analysis of a continuous variable, the normality of data should be examined. Describe the name and result of the particular method to test normality.

D. When analyzing a categorical variable, if the number of events and sample is small, exact test or asymptotic method with appropriate adjustments should be used. The standard chi-squared test or difference-in-proportions test may be performed only when the sample size and number of events are sufficiently large.

E. The APM strongly encourages authors to show confidence intervals. It is not recommended to present the P value without showing the confidence interval. In addition, the uncertainty of estimated values, such as the confidence interval, should be described consistently in figures and tables.

F. Except for study designs that require a one-tailed test, for example, non-inferiority trials, the P values should be two-tailed. A P value should be expressed up to three decimal places (ex. P = 0.160 not as P = 0.16 or P < 0.05). If the value is less than 0.001, it should be described as “P < 0.001” but never as “P = 0.000.” For large P value greater than 0.1, the values can be rounded off to one decimal place, for example, P = 0.1, P = 0.9.

G. A priori sample size calculation should be described in detail. Sample size calculation must aim at preventing false negative results pertaining to the primary, instead of secondary, endpoint. Usually, the mean difference and standard deviation (SD) are typical parameters in estimating the effect size. The power must be equal to or greater than 80 percent. In the case of multiple comparisons, an adjusted level of significance is acceptable.

H. When reporting a randomized clinical study, a CONSORT type flow diagram, as well as all the items in the CONSORT checklist, should be included. If limited in terms of the space of the manuscript, this information should be submitted as a separate file along with the manuscript.

I. Results must be written in significant figures. The measured and derived numbers should be rounded off to reflect the original degree of precision. Calculated or estimated numbers (such as mean and SD) should be expressed in no more than one significant digit beyond the measured accuracy. Therefore, the mean (SD) of cardiac indices in patients measured on a scale that is accurate to 0.1 L/min/m² should be expressed as 2.42 (0.31) L/min/m².

J. Except when otherwise stated herein, authors should conform to the most recent edition of the American Medical Association Manual of Style.

Discussion

The discussion should be described to emphasize the new and important aspects of the study, including the conclusions. Do not repeat in detail the results or other information that is provided in the introduction or the results section. Describe the conclusions according to the purpose of the study but avoid unqualified statements that are not adequately supported by the data. Conclusions may be stated briefly in the last paragraph of the discussion section.

Acknowledgments

Persons or institutes that contributed to the manuscript but not sufficiently to be coauthors may be recognized. Financial support, including foundations, institutions, pharmaceutical and device manufacturers, private companies, or intramural departmental sources, or any other support, should be described.
References

- References should be obviously related to documents and should not exceed 30. References should be numbered consecutively in the order in which they are first mentioned in the text. Provide citations in the body text. All references should be listed in English, including author, title, name of journal, etc.

- The format for references follows the descriptions below. Otherwise, it follows the NLM Style Guide for Authors, Editors, and Publishers (Patrias, K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling, DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007 [updated 2015 Oct 2; cited Year Month Day]. Available at: www.ncbi.nlm.nih.gov/books/NBK7256/).

- If necessary, the Editorial Board may request original documents for the references.


- Six authors can be listed. If there are more than 6 authors, only list 6 names with "et al."

- Provide the start and final page numbers of the cited reference.

- Abstracts of conferences may not be included in the references. The American Society of Anesthesiologists (ASA) refresher course lecture is not acceptable as a reference.

- Description format

A. Regular journal


B. Monographs

- If reference page is only 1 page, mark ‘p.’
- Note if it is beyond the 2nd edition.


- Translated documents cannot be used as references. The original documents should be provided as references.

C. Chapter

Any separate author of a chapter should be provided.


D. Electronic documents


E. Online journal article


F. Advance access article


Tables

- Only one table is to be drawn per page in the order cited in the text.
- The title of the table is to be in English and written at the top of the table in the form of a phrase.
- Words in the table excluding the title should use capital letters for the first word, and the following words are to be written in small letters.
For demographic data, gender is recorded as M/F, age as yr, (if necessary, use days or months in children) without decimal point. The “±” sign within the table is to be aligned with the rows above and below.

Footnotes are to be written in the following order: “Values are mean ± SD (or SEM) or median (1Q, 3Q),” the explanations for the groups and the abbreviations in order of appearance, and statistics. Abbreviations apart from internationally recognized abbreviations are to be explained with their full spellings at the bottom of the table. Full spellings are to be presented even for repeated abbreviations for each table in order of appearance.

Significance marks are to conform to the Vancouver style (Uniform Requirements for Manuscripts Submitted to Biomedical Journals. JAMA 1997; 227: 927-34). In other words, these must be in the order of *, †, ‡, §, •, ‣, ․, ․•, ․••, ․••• and written as superscripts.

Legends for figures and photographs

All of the figures and photographs should be described in the text separately.

The description order is the same as in the footnotes in tables and should be in recognizable sentences.

Define all abbreviations every time they are repeated.

APM encourages authors to use color to increase the clarity of figures. Please note that color figures are used without charge.

Standard colors should be used (black, red, green, blue, cyan, magenta, orange, and gray). Avoid colors that are difficult to see on the printed page (e.g., yellow) or are visually distracting (e.g., pink). Figure backgrounds and plot areas should be white, not gray. Axis lines and ticks should be black and thick enough to clearly frame the image. Axis labels should be large enough to be easily readable, and printed in black.

Figures should be uploaded as separate tif, jpg, pdf, gif, or ppt files. Width of figure should be 84 mm (one column). Contrast of photos or graphs should be at least 600 dpi. Contrast of line drawings should be at least 1,200 dpi. Number figures as “Fig. (Arabic numeral)” in the order of their citation (ex. Fig. 1).

Photographs should be submitted individually. If Fig. 1 is divided into A, B, C, and D, do not combine it into 1, but submit each of them separately. Authors should submit line drawings in black and white.

In horizontal and vertical legends, the letter of the first English word should be capitalized.

Connections between numbers should be denoted by “–,” not “~.” Do not space the numbers (ex. 2–4).

An individual should not be recognizable in photographs or X-ray films unless written consent has been obtained from the subject and is provided at the time of submission.

Pathological samples should be pictured with a measuring stick.

The APM publishes supplemental video (movie) clip(s) that will be available online. Authors should submit videos according to our video submission guidelines.

Each video clip should clearly illustrate the primary findings within an adequate amount of viewing time and should be discussed in the text. Authors should provide appropriate labeling (e.g., arrows, abbreviations of anatomic structures, etc.) in the video clips. However, all identifying information, including patient names and/or ID numbers, hospital names, and dates of the procedures, should be removed.

Video clips should contain succinct teaching points that must be supported by the current literature or standard reference texts, preferably those most accessible to the general reader. The adequacy of the teaching points will be evaluated during the review process and finally confirmed by the Editorial Board at the end of the review process.

Video clips are uploaded as the last file(s) at the time of manuscript submission and should be marked as supplementary video files.

The video clip(s) should have simple file names (e.g., Video 1, Video 2) and should include the appropriate extension (e.g., .mov, .mpg, .avi).

The maximum number of video clips is 20.

The video clip(s) should be playable on Microsoft Windows OS. The video clip(s) should be tested for playback before submission, preferably on computers not used for their creation, to check for any compatibility issues.

Individual video files should be a minimum of 480 × 320 pixels (smaller clips will not be accepted) and a maximum of 2 GB. Files of < 15 MB will be rejected outright unless special arrangements have been made with the editorial board prior to submission. Approval of files of > 2 GB will be made at the end of the review process.

Supplemental still images that correspond to the re-
spective video clip(s) should be, but are not always required to be, accompanied by legends. The video clip file name(s) should refer to the corresponding figure number(s).

9. The author will be able to find additional information in the Figures and photographs section.

2) Case Reports
A case report is almost never a suitable means to describe the efficacy of a treatment or a drug; instead, an adequately powered and well-controlled clinical trial should be performed to demonstrate such efficacy. The only context in which a case report can be used to describe efficacy is in a clinical scenario, or population, that is so unusual that a clinical trial is not feasible. Case reports of humans must state in the text that informed consent to publication was obtained from the patient or guardian. Copies of written informed consents should be kept. If necessary, the editor or reviewers may request copies of these documents. If these steps are impossible, Institutional Review Board approval should be obtained prior to submission. Rarity of a disease condition is itself not an acceptable justification for a case report.

(1) Cover page: Same as that for clinical and experimental studies.

(2) Abstract: All case reports should contain a structured abstract that is written only in English. Provide an abstract of no more than 150 words. It should contain 3 subsections: Background, Case, and Conclusions. A list of keywords, with a minimum of 3 and maximum of 10 items, should be included at the end of the abstract.

(3) Introduction: Should not be separately divided. Briefly describe the case and background without a title.

(4) Case report: Describe only the clinical information that is directly related to the diagnosis and anesthetic management.

(5) Discussion: Briefly discuss the case, and state conclusions at the end of the case. Do not structure the conclusion section separately.

(6) References: The number of references should be less than 15. However, if necessary, the number of reference can be added in accordance with the decision of the editorial committee.

(7) Tables and figures: Proportional to those for clinical and experimental studies.

3) Reviews
Review articles synthesize previously published material into an integrated presentation of our current understanding of a topic. Review articles should describe aspects of a topic in which scientific consensus exists, as well as aspects that remain controversial and are the subject of ongoing scientific disagreement and research. Review articles should include unstructured abstracts written in English equal to or less than 250 words. The organization should be in order of abstract, introduction, text following each title, conclusion and references. Figures and tables should be provided in English. Body text should not exceed 30 A4-sized pages, and the number of figures and tables should each be less than 6. However, if necessary, the number of pages, number of figures and tables can be added in accordance with the decision of the editorial committee.

4) Letters to the Editor
Letters to the Editor should include brief constructive comments that concern previously published articles and interesting cases. Letters to the Editor should be submitted no more than 3 months after the paper has been published.

(1) Cover pages should be formatted in the same way as those of clinical research papers. The corresponding author should be the first author. A maximum of five authors is allowable.

(2) The body text should not exceed 1,000 words and should have no more than 5 references. A figure or a table may be used.

(3) Letters may be edited by the Editorial Board, and if necessary, responses by the author of the subject paper may be provided.

5) Book reviews and announcements
Book reviews as well as news of scientific societies and scientific meeting dates in Korea or abroad can be included. Their formats will be same as those of Letters to the Editor.

6) Images and Videos in APM
This feature is intended to capture the sense of visual discovery and variety that anesthesiologists experience.

(1) The title should contain no more than 8 words. No more than 2 authors should be listed.

(2) The legend should contain no more than 250 words.

(3) If there is more than one panel, please label them Panel A, Panel B, etc.

(4) The legends to the images and videos should briefly present relevant clinical information, including a short description of the patient’s history, relevant physical and laboratory findings, clinical course, response to treatment (if any), and condition at the last follow-up.
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**Article title:**

**Author(s):**

(In identical order to the electronic submission and the corresponding author should be underlined)

**Journal: Anesthesia and Pain Medicine**

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Abstract

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8. Should be fewer than 250 words.

Contents: (Introduction-Discussion)

9. Background (referenced), objective. The introduction should give a concise account of the background and purpose of the investigation.
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