Fluid management in patients undergoing neurosurgery

Possible roles of platelets in liver transplantation: regeneration and cancer recurrence

Nasotracheal intubation for airway management during anesthesia

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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 Cardiopulmonary and Vascular Anesthesiologists (KCSVVA), Korean Society of Transplantation Anesthesiologists (KSTA), The Korean Spinal Pain Society (KSPS), Korean Society of Regional Anesthesia (KSR), 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.

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INTRODUCTION

Fluid management is part of the basic care in many clinical situations. Perioperative fluid therapy in patients undergoing neurosurgery is a vital component of anesthetic practice and critical care. There is increasing evidence that intraoperative fluid therapy may influence postoperative outcomes [1–3].

The main purpose of fluid management in neurosurgical anesthesia is to prevent brain damage caused by inadequate cerebral perfusion and provide a good surgical environment. Therefore, it is essential to maintain hemodynamic stability and proper cerebral perfusion pressure during neurosurgery.

Hemodynamic alterations and electrolyte imbalances often occur during neurosurgery because of the frequent use of diuretics to relieve increased intracranial cerebral pressure and edema. In addition, depending on the type of surgery, large amounts of fluids may need to be administered to correct preoperative hypovolemia and perioperative unstable hemodynamics, and prevent cerebral vasospasm.

An extensive debate about the choice and optimal dose of fluid for hemodynamic stability and improved outcomes exists. This review is intended to assist in the clinical applications and research on fluid therapy during neurosurgery by reviewing recent issues and literature on perioperative fluid management practices in various surgical fields, including neurosurgery.

CHOICE OF FLUID IN NEUROSURGICAL PATIENTS

The general principle of fluid therapy for neurosurgery is to maintain normal blood volume and prevent a decrease in plasma osmolarity. In a normal blood-brain barrier (BBB), the movement of water between the plasma and brain is mainly influenced by the osmotic gradient. Therefore, in...
neurosurgery, the osmolarity of the fluid is the most important factor to prevent cerebral edema.

A crystalloid fluid contains small molecular substances without high molecular substances, and it is classified as hypotonic, isotonic, or hypertonic according to its osmolarity. Lactated Ringer’s solution (LR), a commonly used crystalloid, is hypotonic at 273 mOsm/L. Low plasma osmolarity can cause cerebral edema. Therefore, hypotonic solutions, such as LR, are avoided, while normal saline (NS) has traditionally been used as the main fluid in patients with neurosurgery [4].

Since a reduction in oncotic pressure without changing the osmolarity increases cerebral edema in animal models of brain injury [5], colloid solutions have been known to prevent the severe reduction of colloidal oncotic pressure when used appropriately. However, the European Society of Intensive Care Medicine (ESICM) task force recommended against the use of colloids in patients with brain injury [6], continuing the debate about the use of colloids in neurosurgery.

**Crystalloid solutions**

Hypotonic solutions, such as the LR solution, are avoided in neurosurgical patients to minimize cerebral fluid accumulation. In contrast, NS, an isotonic crystalloid, has been widely used in neurosurgery because it is thought to reduce the risk of cerebral edema [7]. However, since NS has equal amounts of sodium and chloride (154 mEq/L), hyperchloremic metabolic acidosis occurs when a large amount of NS is administered because its chloride concentration is higher than the normal plasma chloride concentration (96–106 mEq/L).

Numerous laboratory and clinical studies have reported a dose-dependent association between hyperchloremia and the use of NS [8–10]. Hyperchloremic acidosis is associated with acute kidney injury (AKI) during abdominal surgery [9]. In a large, propensity-matched retrospective study of 22,851 patients who underwent a non-cardiac surgery, postoperative hyperchloremia resulted in acute metabolic acidosis, leading to increased 30-days mortality and length of hospital stay [10]. A large retrospective study on abdominal surgery showed that patients treated with balanced crystalloids had better outcomes, including mortality, postoperative infection, need for renal replacement therapy (RRT), need for transfusions, electrolyte imbalance, and acidosis than those treated with NS [9].

Meanwhile, the adverse outcomes of NS were not observed in a randomized control study of critically ill patients [11,12], non-critically ill patients [13], and postoperative patients who underwent neurosurgery [14]. In a recent meta-analysis, the balanced crystalloid solution was beneficial in significantly reducing postoperative hyperchloremia and metabolic acidosis, but the evidence was insufficient to compare the effects of buffered and non-buffered crystalloids on mortality and organ failure [15].

In contrast, balanced salt solutions (BSSs) replace chloride ions with lactate, acetate, and gluconate, which prevents the occurrence of hyperchloremic metabolic acidosis [16]. A BSS is the most common choice of resuscitation fluid in clinical practice [17]. In patients who underwent craniotomy, the NS group had higher sodium and chloride levels and had more patients with marked acidosis than in the BSS group [18].

However, though LR is a balanced crystalloid solution, it is hypotonic. A decrease of 1 mOsm/L in the plasma osmolarity results in an increase of 19 mmHg in the pressure of fluid movements across the BBB, and a 3% decrease in the plasma osmolarity results in cerebral edema with a 3% increase in the brain volume and 30% decrease in the intracranial blood cerebrospinal fluid volume [16,19]. Prehospital resuscitation with LR compared to NS was associated with increased mortality in patients with traumatic brain injuries (TBI) [20]. Therefore, LR is not suitable for neurosurgical patients. Instead, isotonic BSS, excluding hypotonic solutions, such as LR, has emerged as a fluid of choice for patients undergoing neurosurgery [21].

An isotonic balanced solution reduces the incidence of hyperchloremic metabolic acidosis and electrolyte imbalances in patients with brain injury, but the intracranial pressure is not different compared with NS [22]. Although a balanced solution has a clear benefit of reducing hyperchloremic metabolic acidosis, its advantage of reducing morbidity and mortality is not clear and requires evaluation.

High-quality data comparing NS and balanced solutions in perioperative and neurosurgical patients are not yet available. Based on the above evidence, although evidence is still lacking, an isotonic balanced solution is preferred over NS in neurosurgical patients because of the lower risk of metabolic acidosis and renal injury.

**Colloid solutions**

Large insoluble molecules in colloid solutions increase...
the intravascular oncotic pressure. In an animal model of brain injury, oncotic pressure reduction without changing the osmolarity increased cerebral edema [5]. Colloid solutions have commonly been used to decrease cerebral edema and improve hemodynamics during neurosurgery [23].

1. Hydroxyethyl starch (HES)

Several randomized trials have shown that HES has adverse effects on kidney function. The routine clinical application of HES in patients with severe sepsis in the VISEP study [24] was associated with higher rates of acute renal failure and RRT than LR. Similarly, two large trials comparing colloids and crystalloids in patients with severe sepsis, the 6S trial [25] and CHEST trial [26], showed an increased incidence of AKI and need for RRT.

In contrast, there was no difference in the incidence of renal failure and mortality between saline and HES 130/0.4 in patients with severe sepsis in the CRYSMAS trial [27]. Likewise, the CRISTAL study, a large, randomized trial, [28], compared the effects of colloids and crystalloids in critically ill patients with hypovolemia and found no significant differences in the 28-day mortality and need for RRT.

Due to the conflicting results, a systematic review and meta-analysis that included the above trials concluded that HES significantly increased the risk of mortality and AKI in critically ill patients [29]. The ESICM task force on colloid volume therapy in critically ill patients recommended against the use of 6% HES 130 in patients with severe sepsis or at risk of AKI. They also recommended not to use colloids in patients with head injuries [6]. Based on accumulating evidence, the European Medicines Agency has restricted the use of HES in critically ill patients, and the United States Food and Drug Administration has added a black box warning. A recent meta-analysis comparing colloids versus crystalloids for fluid resuscitation in critically ill patients showed little or no difference in mortality with moderate-certainty evidence, though starches slightly increased the need for blood transfusion and RRT [30]. However, the heterogeneity of protocols and results in the aforementioned research continues to cause controversy on the recommendations on HES restrictions.

There is some opposing evidence on the restricted use of HES in patients with neurosurgery.

Some animal models and in vitro studies have shown protective effects of HES on the BBB [31–33]. Two early randomized control trials comparing HES with crystalloid solutions in patients with ischemic stroke reported no differences in the safety, hemodynamic efficacy, and complication rates [34,35].

HES has been sometimes used to maintain an optimal volume status to prevent delayed cerebral ischemia (DCI) due to cerebral vasospasm following a subarachnoid hemorrhage (SAH) as a component of the triple H-therapy. Compared to the standard therapy group, the goal-directed fluid therapy (GDFT) with a HES bolus group showed reduced frequencies of vasospasm and cardiopulmonary complications [36]. A recent retrospective study compared SAH patients who received HES with those who received crystalloids and found no significant difference in RRT [37]. Another retrospective study showed no positive correlation between the cumulative doses of HES and serum creatinine in SAH patients who had a normal renal function and concluded that the administration of HES 6% 130/0.4 is safe in SAH patients without pre-existing renal insufficiency. However, caution is warranted in the period of repetitive administration of contrast media [38]. It is noteworthy that the incidence of AKI did not increase despite the substantial amount of HES used in the above trials.

However, there is still no evidence of the superiority of the use of HES in patients undergoing neurosurgery. The possible negative effects, such as renal injury and coagulopathy, should be considered, and HES should be used with caution in neurosurgical patients, in line with the do not harm principle.

2. Albumin

In animal studies, high-concentration albumin therapy improved local cerebral blood flow (CBF), reduced infarct size and brain swelling, and improved neurological function [39–41]. In a retrospective study of patients with SAH, there was a higher proportion of patients with good outcomes at 3 months in the albumin group than in the non-albumin group, although there was no significant difference in the incidence of symptomatic vasospasm [42].

However, the SAFE trial, a multicenter, randomized, double-blinded trial, compared 4% albumin and NS in critically ill patients and showed no significant difference in the outcomes, such as mortality, proportions of organ failures, duration of intensive care unit (ICU) stay, duration of hospital stay, duration of mechanical ventilation, and duration of RRT [43]. However, in the subgroup analysis, the relative risk (RR) of death of trauma patients in the albumin group compared to the saline group (RR = 1.36) was higher than that in the patients without trauma (RR = 0.96). This difference in
the RR of death was because more brain injury patients were assigned to the albumin group than to the saline group.

A post-hoc analysis of a subgroup of patients with TBI in the SAFE trial, the SAFE-TBI study, showed that the 2-year mortality of patients with severe brain injury was significantly higher in the albumin group than in the saline group [44]. A post-hoc follow-up analysis of severe TBI suggested that increased intracranial pressure may have contributed to the high mortality in the albumin group [7]. The results of the SAFE trial and post-hoc analysis continue to influence albumin use in patients with TBI [45].

However, these results should be considered with caution. The SAFE-TBI trial has its own limitations in post hoc subgroup analysis. The mortality of TBI patients was not the primary endpoint of the SAFE trial, and the trial design was not randomized for TBI analysis. Furthermore, the 4% human albumin used in the SAFE study is a hypo-osmolar solution that may potentially increase the intracranial pressure and cause cerebral edema [46].

Experimental SAH models on animals have demonstrated the beneficial effects of albumin [39,47,48], and there has been some evidence on the beneficial effects of albumin in SAH patients [49,50].

The ALISAH trial [49], designed to determine the feasibility and safety of albumin administration in SAH patients, was terminated as two serious complications of pulmonary edema were reported. Patients receiving 1.25 g/kg/d of 25% albumin for 7 days demonstrated better neurological outcomes than those receiving a lower dose. Follow-up analysis of the ALISAH trial showed that higher doses of albumin were associated with a lower incidence of vasospasm, DCI, and cerebral infarction [50]. However, these results should be interpreted with caution. The said trial had an inadequate sample size and insufficient power because it was not designed to study the beneficial effects of albumin.

The ALIAS pilot trial suggested that high-dose albumin therapy has potential neuroprotective effects after ischemic stroke [51]. However, the ALIAS part 1 trial was suspended after safety analysis revealed an increased incidence of pulmonary edema and mortality [52]. The ALIAS part 2 trial, which was modified by adding exclusion criteria and safety measures, was also suspended because of the high incidence of pulmonary edema in the albumin group [53]. The pooled analysis of the data from the ALIAS part 1 and 2 trials showed no difference in the 90-day neurological outcomes and mortality between the 25% albumin and saline groups. However, there was an increased risk of pulmonary edema and intracerebral hemorrhage in the patients administered with albumin 25% at 2 g/kg [54]. Based on this evidence, the ESICM recommends against the use of high-dose albumin in patients with acute ischemic stroke and the use of low (4%) or high-dose (20–25%) albumin in neurointensive care patients [55].

Although controversies still exist based on the above evidence, the use of albumin in the perioperative period of neurosurgery remains questionable. The potential risks and benefits of albumin administration should be assessed on a case-by-case basis.

**HOW TO ADMINISTER THE OPTIMAL AMOUNT OF FLUIDS IN NEUROSURGICAL PATIENTS**

The primary goal of perioperative fluid management during neurosurgery is to maintain hemodynamic stability and an adequate CBF. There is a growing body of evidence that intraoperative fluid therapy influences postoperative outcomes [1–3].

**Restrictive versus liberal fluid therapy in major surgeries**

Traditional intraoperative fluid regimens, which include preoperative dehydration, third space loss, and insensible loss, tend to induce a positive fluid balance that is related to postoperative complications [1].

In the recent decade, several randomized controlled studies have compared restricted fluid therapy with liberal fluid therapy in patients undergoing major abdominal surgeries. Brandstrup et al. [2] showed that patients in the liberal group gained body weight and had more complications than the restrictive group.

After this trial, numerous studies on abdominal surgery showed positive results for restricted fluid therapy, leading to a gradual shift to the trend of using fluid restriction during surgery with the concept of zero-balance. However, in two large observational studies, the zero-balance concept has been concerning due to the possibility of worse outcomes, including AKI associated with excessive restriction [56,57].

Recently, RELIEF trial compared restrictive fluid therapy while maintaining perioperative zero balance with liberal fluid therapy [3]. The results showed that the patients in the restriction group had increased rates of surgical site infection and high risks of AKI.
Based on this recent evidence, worse perioperative outcomes have been observed in patients with both overhydration and excessive fluid restriction. Therefore, fluid optimization is essential for perioperative fluid management. It should also be noted that the amounts of administered volume in the liberal and restricted volume therapies were inconsistent and slightly different for each study [58]. In particular, the postoperative weight gain of the restrictive group in an earlier study by Brandstrup et al. [2] was comparable to the liberal group of the RELIEF study [3]. As such, an excessive restriction can result in worse outcomes, such as AKI.

**GDF T based on dynamic parameters**

To achieve the optimal fluid volume status, it is essential to avoid overhydration and excessive restriction and develop individually optimized fluid regimens using objective parameters. These objective parameters should be targeted preoperatively and measured perioperatively.

GDF T, a recently emerging fluid regimen, is a type of fluid administration that optimizes pre-defined targets based on directly measured hemodynamic parameters (Fig. 1), such as the cardiac output, stroke volume (SV), stroke volume variation (SVV), pulse pressure variation (PPV), systolic pressure variation (SPV), pleth variability index (PVI), and other factors [1].

Favorable outcomes and decreased costs have been shown for patients who underwent GDF T during a major abdominal surgery [59–61]. Although the certainty of the evidence was very low, a meta-analysis comparing GDF T and restrictive fluid therapy in major non-cardiac surgeries showed that the mortality was slightly low in the GDF T group, and there were no differences between the two groups in the complication rate and length of hospital stay [1]. Unlike other studies, including this meta-analysis, one study [62] found that the total infused volume was higher in the restrictive group (basal crystalloid infusion ranging from 4 to 10 ml/kg/h) than in the GDF T group. A limitation of this meta-analysis was the lack of a definition of restrictive fluid therapy. GDF T consists of a given basal infusion and repeat-

![Fig. 1. Dynamic parameters derived from the arterial pressure wave. Mechanical ventilation induces periodic changes in the arterial waveform. Various parameters are derived from this periodic change. Pulse pressure (PP) is the difference between the systolic and diastolic pressures. The area under curve of the arterial pressure wave represents the stroke volume (SV). Systolic pressure variation (SPV) is the difference between the maximum and minimal systolic pressures. SPV consists of two components, delta up (Δup) and delta down (Δdown), by reference pressure (Pref). Pref is the systolic pressure measured at the end of expiration or during apnea. PPV: pulse pressure variation, SVV: stroke volume variation.](www.anesth-pain-med.org)
ed boluses of fluids (usually colloids) to achieve a predefined target. The basal infusion rate is particularly important to compare GDFT with other fluid regimens.

**GDFT during neurosurgery**

In two retrospective studies of patients with SAH, a positive net fluid balance was independently associated with poor outcomes [63,64]. However, as it is difficult to compare restrictive and liberal fluid therapies in neurosurgical patients who must maintain euvolemma, recent studies on GDFT have been conducted. There have been some studies to optimize fluid administration using continuously measured dynamic parameters, such as SVV, PPV, and PVI for patients undergoing neurosurgery.

The SVV is a sensitive predictor of fluid responsiveness before and during brain surgery [65–67]. After the induction of anesthesia and before the start of the surgical procedure, the SVV more sensitively predicted an increase of more than 10% in the SV by LR solution infusion compared to the mean arterial pressure, heart rate, cardiac output, and central venous pressure (CVP) in neurosurgical patients [65]. An SVV of 9.5% was concluded as the optimal threshold (sensitivity: 78.6%, specificity: 93%) for predicting a > 5% increase in the SV after a 100-ml colloid solution infusion [66]. The target of the SVV of GDFT can affect clinical outcomes for supratentorial brain tumor resection [67]. Comparing two GDFT regimens for supratentorial tumor resection (with threshold SVV values set at 10 for the low SVV group and at 18 for the high SVV group), the low SVV group had lower postoperative serum lactate levels, shorter length of ICU stay, and a lower incidence of postoperative neurologic events than the high SVV group [67]. Comparing the GDFT group managed fluid by hemodynamic parameters including the SVV with the control group managed fluid by the therapeutic decision of the attending anesthesiologist, the former had less administered fluids, shorter length of ICU stay, lower ICU costs, and lower lactate levels than the control group [68].

The PPV and PVI have also been reported to be good predictors of fluid reactivity during brain surgery [69–72]. Between the CVP group, which maintained a CVP of 5–10 cm H₂O, and the PPV group, which maintained a PPV below 13%, in patients undergoing a brain tumor surgery, the latter had better postoperative hemodynamic stability and less postoperative fluid requirement [69]. The PPV-guided GDFT during supratentorial tumor resection had a comparable brain relaxation scale, low serum lactate levels, more intra-operative fluids, and higher urine output than the standard care group [70]. In the sitting position for neurosurgery, measuring the PPV and PVI with an ear sensor predicted fluid responsiveness well, but the PVI could not be predicted with a finger sensor. However, the PVI measured with an ear sensor was limited by an unreliable signal in 26% of the patients [71].

A study on children undergoing neurosurgery showed different results. Comparing the PVI, ΔVpeak (respiratory variations in aortic blood flow peak velocity), arterial pressure, CVP, heart rate, inferior vena cava diameter, SPV (including delta up [Δup] and delta down [Δdown]), and PPV in pediatric patients undergoing neurosurgery, the PVI and ΔVpeak predicted the fluid response well, but the PPV and other static and dynamic parameters were reported to be unpredictable [72].

Considering that hemodynamic changes are relatively common in neurosurgery, GDFT, which provides individualized optimal fluid status, is a promising fluid management strategy.

**CONCLUSION**

Despite numerous studies on perioperative fluid management, there is insufficient evidence to draw definitive conclusions regarding fluid management in neurosurgical patients.

Although evidence is still lacking, isotonic balanced crystalloid solutions should be considered the first-choice fluid, while hypotonic solutions should be avoided. Furthermore, colloid solutions should be used with caution, and their potential risks and benefits should be considered.

To achieve an optimal fluid volume status while avoiding overhydration and excessive restriction, the amount and duration of fluid administration should be considered, and an individualized fluid strategy is recommended using GDFT based on dynamic fluid parameters.

**CONFLICTS OF INTEREST**

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

**DATA AVAILABILITY STATEMENT**

Not applicable.
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INTRODUCTION

Platelets have long been considered to play an important role in plug formation and wound sealing following tissue breakage secondary to injury. However, recent research has further suggested that platelets play a critical role throughout the tissue repair process aside from plug formation, with extensive experimental evidence elucidating their involvement in cancer metastasis [1-3]. Platelets are versatile cells involved in many biological processes, such as stimulating inflammation, alerting immune cells, attacking microbial pathogens, and shaping the vascular system [1]. On the other hand, platelets are also known to play certain roles in disease conditions, such as in the development of stroke, heart attack, and rheumatoid arthritis, among others [1]. Therefore, among these various functions, the current mini review focused on the role of platelets in tissue regeneration and metastasis.

PLATELETS IN POST-TRANSPLANT LIVER REGENERATION

Platelets primarily accumulate at the site of tissue damage, wherein vascular defects are sealed as part of the coagulation cascade. Furthermore, they release a large number of biologically active mediators at these injury sites, which initiate or modulate damaged tissue regeneration. Moreover, extensive experimental evidence has elucidated the involvement of platelets in tumor growth and metastasis. As such, this mini-review aimed to highlight the relatively lesser known functions of platelets.

Keywords: Hepatocellular carcinoma; Liver regeneration; Living donors; Metastasis; Recurrence; Transfusion-related acute lung injury.
in which platelet-released mediators were found as the most important contributors for the initiation of hepatocyte proliferation [6–10]. In particular, previous studies performed in rats showed that plasma HGF concentration rose immediately and liver HGF receptor was activated within 30 min after hepatectomy, whereas the intrahepatic HGF reserve was rapidly consumed during the first three hours after hepatectomy [11,12]. Additionally, other platelet-released mediators, such as serotonin, were also known to be important in initiating mitogenic signaling and triggering hepatocyte proliferation [9,10]. Given this evidence, it could be deduced that the presence of a sufficient number of functioning platelets to deliver and release mediators to the graft immediately after liver graft reperfusion is crucial in liver transplantation, particularly in living donor liver transplantation requiring quantitative liver regeneration [13]. The positive association between intraoperative platelet transfusion and graft regeneration in our research team’s recent study also supports this hypothesis [14,15]. To date and to the best of our knowledge, this study was the first to identify the importance of intraoperative platelet transfusion during living donor liver transplantation [14]. Particularly, our results have clinical relevance since intraoperative platelet transfusion was clearly reported to be beneficial for graft regeneration in recipients with an increased risk of liver failure, such as those with macrosteatotic or small-for-size grafts. In contrast to our study showing no negative intraoperative platelet transfusion effects, two previous studies performed in a transplant center demonstrated negative impacts of intraoperative platelet transfusion on post-transplant mortality [16,17]. Putative reasons for these discrepant outcomes were thought to be attributable to the differences in graft type (living donor vs. deceased donor), platelet process (leukoreduction and irradiation) [18,19], transfusion indication (so-called rescue strategy: platelets were never indicated solely based on platelet counts and were always given after excessive blood loss occurred) [14], and hemostatic agent (routine aprotinin use) [20]. Apart from platelet transfusion, we also identified the importance of immediate post-reperfusion platelet counts measured during the reperfusion phase of living donor liver transplantation, which was consistent with a recent study of patients undergoing hepatectomy, suggesting that immediate postoperative platelet count was a predictor of liver regeneration [21]. Studies have shown that platelet counts during liver transplantation tend to decrease considerably according to blood loss (progressive coagulopathy and surgical bleeding) and hemodilution (fluid infusion and transfusion). In this regard, transplant teams should make efforts to maintain adequate platelet count levels during the critical period when diverse signals trigger liver regeneration. Moreover, these findings were consistent with a previous study in rats demonstrating that platelet-rich plasma infusion immediately after 70% hepatectomy promoted mitogenic signaling pathways for the first 4 h postoperatively, which was connected to improved early hepatocyte proliferation and liver mass recovery [22]. The authors of that study also suggested that platelet administration might be an innovative therapeutic strategy for liver regeneration in small-for-size liver transplantations.

The liver’s remarkable ability to regenerate has allowed the possibility for living-donor liver transplantation to become a reality; however, this procedure has also been found to involve the potential risk of liver failure resulting from insufficient graft regeneration. Therefore, liver regeneration is a key element in the success of living donor liver transplantation. Particularly, liver regeneration is orchestrated by the interplay between various cells and mediators, of which platelet-derived mediators are known to play important roles. Notably, a landmark study by Lesurtel et al. [9] and certain subsequent studies newly discovered that platelet-derived serotonin mediated liver regeneration [8–10,15], and that triggering regeneration pathway signals occurred immediately after hepatic tissue injury, such as functional mass decrease or ischemia-reperfusion injury. More specifically, regeneration of a reduced-size partial liver graft was initiated immediately after graft reperfusion during living donor liver transplantation, and thus the intraoperative post-reperfusion period was considered to be highly critical. In this regard, our recent research showed that intraoperative platelet counts during the post-reperfusion phase and platelet transfusion were significantly associated with the degree of early graft regeneration following living donor liver transplantation [14]. Taken together, we hypothesized that intraoperative platelet counts and platelet transfusion may affect graft regeneration in relation to the serotonin pathway. Given that, we then evaluated the association between intraoperative platelet counts and serum serotonin levels, as well as the effect of intraoperative platelet transfusion on serum serotonin levels in living donor liver transplantation. Indeed, this was the first study to describe intraoperative changes in serum serotonin levels during living donor liver transplantation, measured using liquid chromatography with tandem mass spectrometry, which has been established highly reliable method. On observation, platelet counts and serotonin
levels moved in the same direction throughout the surgical procedure. An immediate increase during the first hour after graft reperfusion followed by a gradual decrease was also observed, possibly reflecting initial systemic platelet extraction and subsequent hepatic platelet exhaustion [23]. On analysis, platelet counts and serotonin levels showed significant linear correlations. In healthy individuals, more than 95% of serotonin exists in the platelet, resulting in almost similar serum serotonin and intraplatelet serotonin levels [24,25]. In our findings, this similarity in the intraoperative movement of platelet counts and serum serotonin levels combined with the linear correlation between them indicated that most serotonin existed in platelets and were delivered by them in liver transplant recipients, resulting in platelet counts and serum serotonin levels that were physiologically similar to healthy individuals [10]. Therefore, our findings supported the hypothesis that the association between platelet count and early graft regeneration after living donor liver transplantation may be mediated by serotonin [14]. In addition, the platelet transfusion dose for cirrhotic patients was unknown despite its clinical importance [26]. We found that 1 unit of apheresis platelets, which corresponds to 6 units of whole blood platelets, increased platelet counts by 30 × 10^9/L, which was the amount expected in healthy persons. This immediate increase in serotonin levels following platelet transfusion also supported the hypothesis that the association between platelet transfusion and early graft regeneration after living donor liver transplantation may be mediated by serotonin. However, it should be noted that platelet-mediated liver graft regeneration was mediated by other various cytokines and growth hormones aside from serotonin [6–8,10]. Thus, further studies are warranted to distinguish the respective roles of serotonin from other platelet-derived molecules, such as HGF, vascular endothelial growth factor, and insulin-like growth factor-1.

PLATELETS IN POST-TRANSPLANT METASTASIS AND TUMOR RECURRENCE

Liver transplantation has been a well-established therapeutic option for hepatocellular carcinoma (HCC) treatment, addressing both underlying liver diseases, which is considered a premalignant lesion, and a tumor burden. Despite this, many recipients experience tumor recurrence, wherein recurrent HCC becomes a major cause of death for these patients. As mentioned previously, platelets are the primary cells for hemostasis and tissue repair, but extensive experimental evidence has also elucidated their involvement in tumor growth and metastasis [1–3]. More specifically, clinical evidence has demonstrated an association between higher platelet counts with both shorter survival time and increased recurrence after treatment in various solid tumors [27]. In HCCs, a retrospective analysis using a large database of biopsy-proven HCC patients reported a positive correlation between platelet count and tumor size/total tumor mass [28]. Another retrospective cohort study demonstrated that pretreatment platelet count was positively associated with the probability of HCC recurrence after curative treatment [29]. These findings, as well as those from other previous studies, suggested that the relationship between platelets and tumors was not a simple epiphenomenon resulting from tumor-induced thrombopoiesis, but rather a direct contribution of platelets to multiple steps in cancer progression, including tumor cell angiogenesis, protection from immune processes, extravasation, and arrest within the vasculature [2,27,30,31]. In fact, a previous study in hepatitis B transgenic mice clearly demonstrated that antiplatelet treatment reduced intrahepatic inflammatory responses and HCC development with improved long-term survival [32]. Thus, our research team hypothesized that the risk of HCC recurrence after living donor liver transplantation was affected by platelets [33]. Given that, we then evaluated the relationship between preoperative platelet count and post-transplant HCC recurrence, demonstrating the independent association between them. Recurrence risk was greater with higher platelet counts after adjustment for confounders, such as tumor biology and liver disease severity in both the pre- and post-matching cohorts.

Accordingly, the risk of post-transplant HCC-related deaths was also greater with higher platelet counts. Notably, the influence of platelets was consistent regardless of tumor aggressiveness, which was an important finding since a more aggressive tumor biology due to higher platelet counts could be considered a bias. Moreover, the incorporation of platelet count into the Milan criteria significantly increased its predictive power for estimating recurrence, and no inflammation-based scores, including platelet-to-lymphocyte ratio, were superior to preoperative platelet count, which was in agreement with a previous study [34]. Particularly, the platelet-to-lymphocyte ratio was analyzed as significant, despite the insignificance of neutrophil or lymphocyte counts as well as the neutrophil-to-lymphocyte ratio, supporting the importance of platelets per se. In contrast to the surrogate markers, platelets are effector cells directly interacting with cancer cells.
in the metastatic cascade [1–3,27,30,31], in which their association with tumor recurrence appears to be robust and independent in liver transplant recipients, whose systemic inflammation status and platelet counts are both affected by liver disease. Taken together, the results from our study suggested a potentially important role of platelets in HCC metastasis after living donor liver transplantation, as well as demonstrated the following important clinical implications [32,35,36]. First, the decision-making processes of HCC staging and management largely depended on estimated recurrence probability [37]. Our study indicated that HCC management guidelines could be refined by considering platelet counts. Second, the data supported the feasibility of platelet modulation therapies and its selective implication based on platelet count, which has a spectrum of feasible therapies, including cyclooxygenase, protease-activated receptor, and integrin GPIIb/IIIa inhibitors [2,32,35,36,38,39]. Until more scientific data verifying their safety is accumulated, HCC patients with mild thrombocytopenia, in particular, are likely better candidates for these therapies, since such patients can have less bleeding diathesis and greater metastasis risks. Furthermore, the stable late post-transplant phase might provide another time window for targeting latent metastasis, which has a lesser concern on bleeding complications or graft regeneration [13,14]. In that regard, therapies that can differentiate the platelet-cancer loop from coagulation or tissue regeneration pathways represent opportunities to prevent metastasis with minimum related complications. Third, the study suggested that restrictive perioperative platelet transfusion policies might have another advantage from the viewpoint of metastasis prevention [40].

HCC recurrence arises from tumor cells present in the circulation or in micrometastatic colonies following primary tumor removal. To metastasize successfully, disseminated tumor cells must complete multiple complex steps, consisting of survival in the blood stream, adherence to the vascular wall, subsequent extravasation and initial seeding, and lastly, the re-initiation of growth [31]. During this metastatic cascade, platelets interact with tumor cells at every step in circulation, as well as at the site of distant metastases, while directly enhancing invasive potential or indirectly modulating the microenvironment [2,27,41,42]. For example, platelet-tumor cell cross-linking forms a shield around tumor cells and protects them from mechanical destruction by hemodynamic shear forces and immunologic lysis by natural killer cells. Additionally, they also promote tumor cell arrest to the secondary site through rolling and tethering to the vessel wall. Regarding cellular motility, platelet-derived molecules promote extravasation by increasing endothelial permeability and inducing morphological changes from epithelial to mesenchymal transition. Moreover, platelets are known to release proangiogenic growth factors, such as the vascular endothelial, platelet-derived, fibroblast, insulin-like, and transforming growth factors [2,10]. Although extensive experimental research has outlined the platelet-cancer loop, clinical studies also support the importance of platelets by demonstrating an association between platelet count and poor prognosis in cancers of various organs, including the liver [27,29,43]. Interestingly, sorafenib, the first systemic drug to be approved for advanced HCC management, was found to suppresses HCC progression by inhibiting cellular signaling mediated by platelet-derived growth factors, such as the vascular endothelial and platelet-derived growth factors [44].

Furthermore, recent studies have consistently demonstrated that early post-transplant platelet count was mainly determined by preoperative platelet count [45]. Thus, it could be deduced that patients with higher preoperative platelet counts continue to experience greater platelet-tumor cell interactions and consequently a more favorable metastasis microenvironment during early post-transplantation when surgery-induced stress, inflammation, and immunomodulation provide a vulnerable time window. Evidence that circulating tumor cells require only a few hours to days to complete the metastatic cascade further supports the relevance of preoperative platelet count [31]. Additionally, some tumor cells may also remain dormant at the secondary site for a long period, thus initiating growth at a much later time and resulting in a metastasis that occurs over an extended duration [31]. Since post-transplant platelet counts significantly correlated with preoperative values even months or years after transplantation, recipients with higher preoperative platelet counts might have a greater chance of experiencing HCC cell metastasis in much later periods.

Platelet counts in HCC patients are determined by parenchymal liver disease severity and HCC aggressiveness [46]. More specifically, platelet production is decreased mainly due to impaired thrombopoietin synthesis in the diseased liver, whereas platelet destruction is increased due to cirrhosis-related hypersplenism and platelet-associated antibodies. Moreover, systemic inflammation increases platelet consumption and hyperdynamic circulation dilutes platelet concentration [47]. In contrast, solid tumors enhance hepatic thrombopoietin synthesis by releasing thrombopoietic cy-
tokines, wherein more aggressive tumors induce a greater degree of thrombocytosis [27, 48]. Accordingly, parenchymal liver disease status and tumor biology are significantly different according to preoperative platelet counts. Since some determinants of platelet count are also contributors to post-transplant outcomes, the success of the study evaluating the relationship of platelets and post-transplant metastasis mainly depends on determining whether the platelet count is an epiphenomenon. First, there is the possibility of recurrence risk being overestimated in patients with higher platelet counts with a more aggressive tumor biology. Second, there is the possibility of recurrence risk being underestimated in patients with lower platelet counts, since HCC-unrelated death was reported to be greater in this group [33].

Therefore, future studies evaluating the relationship between perioperative platelets counts or platelet transfusion, and post-transplant HCC metastasis or recurrence, should be considered with regards to their potential biasing effects as in our research [33].

CONCLUSION

Liver transplant physicians who perform perioperative platelet transfusion should be aware that platelets are not only cells involved in decreasing the amount of medical bleeding, but they are also in charge of liver regeneration and post-transplant HCC metastasis. The two relatively novel concepts are now being actively studied in various populations, including liver transplant recipients, as presented in this paper. As such, we would like to call attention to research evaluating the potential positive and negative roles of platelets and platelet transfusion in liver transplant recipients for the creation of future studies in this field.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

This is a review article written based on previous studies.

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INTRODUCTION

Airway management plays an important role in the management of critically ill patients, trauma patients, and anesthesia for all surgeries and procedures performed inside and outside of the operating room. From this point of view, anesthesiologists choose and apply various methods such as the bag and mask methods, airways simply inserted into the oral or nasal cavity, supraglottic airway devices, oral or nasotracheal intubation, percutaneous dilated cricothyroidotomy, and tracheostomy according to the patient’s condition and the need for surgery. Among these methods, supraglottic airway devices or orotracheal intubation are usually selected. Nasotracheal intubation is attempted for head and neck surgery, oral surgery, or for keeping the airway safe while preventing further damage in some trauma patients [1-3].

Nasotracheal intubation is a common airway management method used for anesthesia. Since the endotracheal tube is inserted into the trachea through the nasal cavity, it is easier to fix and stabilize through the small diameter of the nasal pathway compared to the oral cavity. It is the preferred method not only for anesthesiologists but also for surgeons who perform surgeries in the head and neck region, especially oropharyngeal, dental, and maxillofacial surgeries, as it helps to improve vision and access for surgery [3-5].

In the nasotracheal intubation process and management, additional instruments, drugs, and skilled maneuvers are required, and with recent developments in techniques and methods, potential problems or complications arising from the blind introduction of the endotracheal tube into the nasal cavity can be avoided [6-9]. Therefore, this study aimed to summarize the latest findings with a literature review regarding nasotracheal intubation. It will include the newly introduced information along with methods that have been developed over the years with accumulated clinical experience and improved instruments to facilitate safe intubation with reduced complications. Therefore, in this review article, we summarize the basic anatomy of the nasal airways to clarify the precautions, delineate the history and development of various methods and instruments, and describe the indications, contraindications, complications, and preventive methods of nasotracheal intubation.

Keywords: Airway management; Anesthesia; Endotracheal intubation; Nasal cavity.
Endotracheal intubation is applied to more than 80% of patients requiring general anesthesia and has been in use for more than 1000 years [10]. Alfred Kirstein introduced direct laryngoscopy in 1895, and Franz Kuhn performed endotracheal intubation to maintain the airway in patients intoxicated with morphine and introduced the nasal route. Guedel and Waters added cuffs to the tubes in 1932 to ensure positive pressure ventilation [10,11].

Nasotracheal intubation was introduced by Franz Kuhn in 1902, suggesting that it would be more physiological than orotracheal intubation. Magill introduced the oral airway or short rubber tube through the nasal cavity to the pharynx to insufflate anesthetics and oxygen on a hospital ship during World War I in 1919. Nasotracheal intubation was attempted to compensate for these shortcomings. However, since there were no adjuvant devices such as a laryngoscope or Magill forceps at this time, various postures (e.g., sitting positions) were attempted according to the skill and preference of the anesthesia providers. A “blind nasal intubation” was performed by inserting a catheter, inspiratory tube, or a tube made of a soft material causing relatively little stimulation to the breathing apparatus [12,13]. It was introduced as an effective method when Rowbothan first attempted oral surgery in the operating room in 1920 [11–14]. At the same time, nasotracheal intubation was introduced as an airway management method that could be effectively applied for long-term care in the intensive care unit, but there was a risk of infections such as sinusitis [15].

In the past, various postures for orotracheal and nasotracheal intubation were applied according to individual technical preferences. Magill first described a sniffing position with the head lifted approximately 15° from a stable supine position in 1936 [13]. Reports on nasotracheal intubation using a fiberoptic bronchoscope began in the 1960s. Instruments such as the video-laryngoscope and Magill forceps, improvement of endotracheal tube materials, and application of vasoconstrictors (e.g., epinephrine and phenylephrine) and lubricants helped facilitate nasotracheal intubation, thereby increasing its success rate [16].

The anatomical characteristics of the airway from the nostril to the trachea, where the tube passes through while attempting nasotracheal intubation, can be described as follows: The nasal cavity refers to the area starting from the anterior nares (nostrils), through the posterior end of the nasal septum, and then through the posterior nasal apertures (choanae) to the nasopharynx in contact with the oropharynx. The skull base and intracranial components are located at the top, and the hard palate in contact with the oral cavity is located at the bottom. The medial wall of the nasal cavity is formed by the nasal septum, which consists of cartilage in the front and bone in the rear. The bony part on the medial surface is connected to the perpendicular plate of the ethmoid bone at the top and the vomer at the bottom [2–5]. The lateral surface is connected to the medial surface of the orbit at the top and the medial wall of the maxillary sinus at the bottom. On the lateral surface, three nasal conchae (turbinates) are curved downward and are composed of bone covered with a thick respiratory mucosa [2–5].

The inferior turbinate is the largest of the three turbinates on both the left and right sides and is firmly fixed on the outer surface, connected to the conchal crest of the maxilla, the descending process of the lacrimal bone, the frontal process of the maxilla, the uncinate process of the ethmoid, and the conchal crest of the palatine bone. If avulsion occurs during nasotracheal intubation despite this tight fixation, the inferior turbinate may be fractured and enter the nasotracheal tube, enter the main bronchus causing an obstruction. The inferior turbinate can be easily observed using a rhinoscope from the outside, but it is difficult to distinguish it from nasal polyps [2–7]. The superior turbinate was the smallest and was located just above and behind the middle turbinate. In addition, it is attached to the skull base upward and the nasal wall on the side [2–6]. The middle turbinate is an integral part of the ethmoid bone, which is loosely attached to the free, convoluted margin of the thin lamella descending from the cribriform plate and the posterior ethmoid air cells in the back. It is mainly responsible for olfaction, humidification, and lubrication, mediated via the olfactory nerve, in the cribriform plate, and controls temperature and humidity in the inhaled air while performing filtration [2–6].

Each turbinate was covered by a thick mucous membrane, and blood was supplied from the anterior ethmoidal artery. The lamina propria of the mucous membrane contains cavernous sinusoids or plexus of large veins and is very vulnera-
ble to trauma. Situations such as traumatic avulsion can lead to massive epistaxis, and excessive force on the turbinate can lead to olfactory nerve injury or fracture of the cribiform plate, which may be accompanied by cerebrospinal fluid (CSF) rhinorrhea [2–6,17].

The upper part of the nasal cavity is narrow and connected with the cribiform plate of the ethmoid, with the lateral wall and septum, distinguishing the nasal cavity from the anterior cranial fossa. The nasal cavity is entirely covered by a respiratory mucosa composed of ciliated pseudostratified columnar epithelium, with many mucous secretions for humidification and entrapment of inhaled impurities [2–7].

The sphenopalatine artery from the maxillary artery is the main blood supply to the nasal cavity. The Kiesselbach’s plexus is formed by anastomosis with the ascending branch of the greater palatine artery and superior labial artery in the anterior part of the nasal septum (Little’s area). In the nasal cavity, mucous membranes and blood vessels play an important role, but they are the main sites of epistaxis that occur naturally and can easily lead to bleeding even with light external trauma [2–7].

Internal structural abnormalities of the nasal cavity are often asymmetric. The most common anatomical abnormality was septal deviation (SD). It is commonly found in the anterior cartilaginous part and rarely in the septum, which consists of bone in the rear. It often occurs due to trauma. However, it can also occur without any specific injury due to fetal intruterine molding or trauma during parturition. In addition, nasal SD may occur due to maldevelopment of the vomeropalatal complex [18]. SD causes a change in airflow, resulting in a change in the mucosal lining. Dryness and ulceration of the mucous membrane and hypertrophy may occur in the convex and concave parts of the inferior turbinate, respectively. These SDs often result in the narrowing of the nasal airway. Severe structural abnormalities are rare but may occur after shock or surgery. Although rare, choanal atresia is a congenital malformation that may occur during childhood [5,6].

In children, it generally takes eight years to develop an airway similar to that of an adult. Because the length of the trachea is relatively short, the change in length according to the flexion and extension of the neck is large, and a tube may be inserted deeply or fall out depending on the flexion and extension of the neck [19,20]. Infants and young children are susceptible to upper respiratory tract obstruction and respiratory failure. Because the length of the trachea is relatively short in children, the endotracheal tube may be displaced into either the endobronchial or cephalad position towards the glottis, according to slight postural changes in flexion or extension of the neck. Airway resistance is increased owing to the selection of small tubes for a relatively smaller airway. Therefore, it should be selected and attempted after understanding the characteristics of the pediatric airway depending on the age and confirming the diameter, length, and characteristics of the endotracheal tube [20].

**NASOTRACHEAL INTUBATION**

**Preanesthetic evaluation**

For each patient requiring anesthesia, anesthesiologists should perform the pre-anesthetic evaluation required for nasotracheal intubation, along with preoperative evaluation.

1. During patient interviews and examinations, the presence or absence of a history of epistaxis, condition of teeth, potential anesthetic problems such as a history of injuries to the face, and potential complications or contraindications to the planned procedure should be identified (e.g., airway disorders, progressive infections including sinusitis, swelling, epistaxis, etc.). In addition, a history of anaphylaxis and allergic reactions to drugs, including drugs used for anesthesia, should be elicited and reviewed. Furthermore, the risks of anesthesia should be based on the patient history and family history of previous surgery and anesthesia (e.g., complications from anesthesia, malignant hyperthermia, etc.) and established standards (e.g., American Society of Anesthesiologists classification of risk), and identifying the need for additional medical consultations and tests in the pre-anesthetic evaluation. Finally, a plan should be established for anesthesia. The induction, maintenance, recovery of anesthesia, postoperative management, and risks and benefits of anesthesia should be discussed with the patient and caregiver.

2. The problems associated with airway management and nasotracheal intubation should be tested and identified (e.g., presence of dentures or loose teeth, limitation of mouth opening, jaw protrusion, length and thickness of the neck, range of motion of the head/neck, etc.), and additional tests such as endoscopy, X-ray, computerized tomography (CT), and magnetic resonance imaging (MRI) should be performed to identify the problems in nasotracheal intubation and prepare for alternative methods. Nasotracheal intubation should be performed based on the overall results of preoperative evaluation. If nasotracheal
intubation is expected to be difficult, a discussion should be conducted with the surgeon to decide whether to perform nasotracheal intubation or not and to devise alternative methods [21,22]. The pre-anesthetic evaluation for these patients should be performed within 48 h before surgery and should be documented and recorded [2–6].

**Considerations for nasotracheal intubation**

1. **Selection of the position of the nostril for intubation**

   The supine position is mostly preferred to perform the orotracheal intubation. However, blind nasotracheal intubation can be performed in the sitting position, depending on the skill of the operator [1–4]. Selecting the nostril to use for endotracheal intubation is an important decision to consider for facilitating intubation and reducing complications. In the pre-anesthetic evaluation, the method of blocking one nostril and breathing on the other side and selecting the comfortable side between them may be the easiest to apply.

   However, as described above, it may be determined according to the shape of the nasal septum by preoperative examination. Although it is possible to select the nostril in most patients using anterior rhinoscopy, it is difficult to accurately determine any abnormalities in the posterior nasal cavity. Nasal endoscopy helps select nostrils for endotracheal intubation and for evaluating intranasal abnormalities. Flexible endoscopy also allows for detailed examination of the entire nasal cavity for nostril selection [2–4]. Depending on the patient’s condition, methods such as facial radiography, CT, and MRI can be used to examine anatomical and pathological abnormalities such as SD [23,24].

2. **Selection of the lower and middle regions of the inferior turbinate in the nasal cavity**

   In nasotracheal intubation, there are lower and upper pathways for passing through the nasal cavity, with the inferior turbinate at the center. The middle turbinate is a thin lamella that is attached to the base of the cribiform plate and is rich in blood vessels. Trauma such as avulsion of the middle turbinate may result in massive epistaxis, CSF rhinorrhea, or damage to the olfactory nerves distributed in the cribiform plate. The lower pathway is the pathway between the floor of the nose and the inferior turbinate. The upper pathway is the pathway between the inferior turbinate and the middle turbinate. Thus, the lower pathway is safer because it avoids trauma to the middle turbinate and cribiform plate [9,17].

**Procedures of nasotracheal intubation**

After all the tests related to surgery and anesthesia were completed, the occurrence of complications during nasotracheal intubation should be reduced. The patient who enters the operating room should be first identified and equipped with monitoring instruments for blood pressure, electrocardiogram, peripheral oxygen saturation (SpO₂), and end-tidal carbon dioxide tension (ETCO₂). Subsequently, management procedures for nasotracheal intubation should be performed.

1. **Premedication**

   Despite the individual differences, sedation or analgesia may be necessary for most patients, as they may exhibit anxiety, particularly if awake intubation is planned. Therefore, drugs such as opioids (e.g., fentanyl, alfentanil, etc.) and sedatives (e.g., benzodiazepine and dexmedetomidine) may be selected depending on the patient’s condition and post-intubation management.

2. **Preparation of the nasal mucosa**

   Commonly used drugs for lubrication and vasoconstriction include lidocaine spray or jelly. It is sprayed at the time of inspiration and enters the glottis to exhibit an effect.

   1) Transtracheal/translaryngeal anesthesia: After checking the cricothyroid membrane between the thyroid and cricoid cartilages with an index finger, a 23 G needle was used with the opposite hand to puncture and aspirate air to check the lumen of the larynx; lidocaine (2%, approximately 2 ml) was injected, and the syringe was removed immediately. The patient may cough during the procedure, and the local anesthetic can provide the effects of applying anesthesia from the epiglottis site to the carina [9]. Transtracheal/translaryngeal anesthesia is preferred for non-general anesthesia and is not necessarily required for general anesthesia [25,26].

   2) Vasoconstrictor: In most cases, lidocaine (3–4%) jelly with phenylephrine (0.05–1%) or epinephrine (1:200,000) added, or oxymetazoline is used to induce vasoconstriction [4–6].

   3) Anti-sialagogues: Before using the airway device, anti-sialagogues (e.g., glycopyrrolate 0.4 mg intramuscularly [IM] or intravenously [IV] / atropine 0.5 ~ 1 mg IM or IV) are used. Excessive secretions can make it difficult to view the laryngoscope and interfere with the effective penetration of local anesthetics into the mucous membrane [2–6].
4) Lubrication of endotracheal tube: Before insertion through the nostril, sufficient lubricant is applied so that the tube can smoothly pass through the relatively narrow nasal cavity. The lubricant is water-soluble, and the addition of local anesthetics such as lidocaine would increase the analgesic effect, while the addition of vasoconstrictors would reduce the risk of bleeding [2–6].

3. Oxygenation

In the entire process of nasotracheal intubation, preoxygenation should be performed with 100% oxygen to the patient before proceeding with the procedure. This increases the body oxygen reserve and delays arterial hemoglobin desaturation because an unexpected situation may arise, resulting in hypoxia, hypoventilation, and loss of airway patency.

Preoxygenation is recommended to ensure that the patient’s end-tidal oxygen concentration is 0.9 or more or the end-tidal nitrogen concentration is 5% or less by tidal breathing [27–29]. Preoxygenation methods include tidal volume × 3 min using a 100% oxygen flow, four deep breaths (vital capacity) within 30 s using a 100% oxygen flow, eight deep breaths within one min using a 100% oxygen flow [27], or the transnasal humidified rapid-insufflation ventilation exchange using the Optiflow high-flow humidified oxygen delivery system [30–32].

4. Anesthesia

Nasotracheal intubation is attempted under general anesthesia with intravenous anesthetic agents or inhaled anesthetics with prior sufficient preoxygenation. Neuromuscular blockers are usually administered after the loss of consciousness for endotracheal intubation under general anesthesia, unless contraindicated or not otherwise required. If neuromuscular blockers are not used for nasotracheal intubation, particular attention should be paid to reduce patient movement, airway irritation, and sympathetic stimulation, because the injury may be invoked during the intubation process [33–35].

5. Insertion through nasal cavity for nasotracheal intubation

The procedure of nasotracheal intubation can be explained by dividing it into three phases: 1) passage through the nose into the pharynx, 2) laryngoscope-guided passage into the glottic inlet, and 3) laryngoscope-guided passage into the trachea [36].

The first phase is explained as follows. An endotracheal tube of appropriate size was selected for the patient, and a lubricant was applied to the site in preparation for insertion. The endotracheal tube was inserted slowly along the bottom of the nasal cavity by pushing it down to the rear through the selected nostril and treated with local anesthesia and vasoconstrictor. While avoiding excessive force, the endotracheal tube should be inserted by rotating it slowly [2–5]. While advancing from the nasal cavity to the oropharynx during the intubation process, resistance may be felt upon passing through the nasopharyngeal junctional space and the posterior nasopharynx. In this case, the endotracheal tube should be inserted while rotating or extending the patient’s neck [37,38].

6. Nasotracheal intubation after insertion through the nasal cavity

In the subsequent process, there may be differences in the insertion method depending on the preference of the anesthesiologist and the patient’s condition. The basic methods are described in this section. In the author’s clinical experience, sometimes more than one attempt of nasotracheal intubation is required in cases of a difficult airway. In such cases, the endotracheal tube inserted into the nasal cavity must be removed and bag-mask ventilation is re instituted while preparing for the next intubation trial. Multiple nasotracheal intubation attempts could hinder subsequent bag-mask ventilation and/or intubation by obscuring the laryngeal view with nasal bleeding and secretions. Therefore, it is necessary to accurately determine the patient’s condition, the degree of difficulty in intubation, and plan to succeed at the first intubation attempt. It is also imperative to prepare adjuvant devices, such as emergency airways and suction devices [39].

1) Blind nasal intubation: Blind nasal intubation is the method used in the past when there is no adjuvant device, in which an endotracheal tube of an appropriate size is selected and prepared by applying a lubricant for insertion. The unanesthetized nostril and lip were blocked, while the chin of the patient was held by the left hand. The endotracheal tube was inserted slowly along the bottom of the nasal cavity by pushing it down to the rear through the anesthetized nostril. While observing the breathing sounds, if the tube is inserted into the pharynx and placed in the middle, it passes under the epiglottis, passes through the vocal cords where the reflex is temporarily stopped by local anesthesia, and is inserted into the larynx. Closure of the glottis can be prevented if the gag reflex
and involuntary swallowing are blocked by appropriate local anesthesia. In conscious patients, pharyngeal muscle tone may help with tracheal intubation. This leads to the endotracheal tube below the epiglottis and into the space between the vocal cords. Endotracheal intubation is mostly performed in the supine position, but in rare cases where intubation is difficult, it may be more effective to perform this in a sitting position [40]. Blind nasal intubation was selected when direct laryngoscopy was difficult or impossible. In recent years, with the advent of flexible fiberoptic endoscopy, which is referred to as the “gold standard technique,” blind nasal intubation has become an old manual technique [41].

2) Nasal intubation using laryngoscope and Magill forceps: Magill forceps were first introduced by Magill in 1920 to guide the nasally inserted endotracheal tube to pass through the glottis under direct or video-laryngoscope visualization [42,43]. When using a video-laryngoscope, there may be some inconvenience due to a lack of skills in the process of intubation while holding the tube with Magill forceps and viewing the video screen [42,43]. If it is difficult to insert the laryngoscope directly through the oral cavity, such as in patients with certain maxillofacial problems, submental intubation may be considered [44].

3) Fiberoptic nasal intubation: Nasotracheal intubation using a fiberoptic endoscope is similar to oral fiberoptic endoscopic intubation. While performing fiberoptic endoscopy, the path through which the endotracheal tube passes through the nasal cavity should be checked in advance. Intubation should proceed to the trachea, and the endotracheal tube should advance through it. However, if the tip of the fiberoptic endoscope is not sufficiently inserted into the trachea, the direction of insertion of the endotracheal tube may deviate. It may be deviated mainly by the epiglottis, arytenoid cartilage, pyriform fossa, or esophagus during insertion. It is possible to insert the endotracheal tube while rotating counterclockwise. In addition, examiners should be careful because the pyriform sinus may look like the glottis under the fiberoptic endoscope [16,45].

Similar to the method of mounting a face mask while applying a fiberoptic endoscope, there is also a method of performing endotracheal intubation; by placing the little finger of one hand at the angle of the mandible, the ring finger at the body of the mandible, the middle finger under the mentum to lift the chin to maintain airway patency and improve the endoscopic view, and by using the thumb and index finger of the same hand to adjust the direction of the fiberoptic endoscope. Flexible fiberoptic intubation is preferred as the main technique for difficult intubation, but it has disadvantages in that it takes time and requires additional equipment as well as skilled maneuvers. However, it facilitates intubation in cases of difficult intubation, avoids damage to surrounding tissues and teeth, improves the view of the larynx, allows the easy decision of the nostril pathway, and causes less bleeding [16,45].

The nasal trumpet may be preferred as it can facilitate intubation or insertion of a fiberoptic endoscope by increasing the diameter of the nostril. However, it cannot be removed after endotracheal intubation and must be held together until extubation. However, this method maintains the airway in patients whose trachea cannot be intubated or who need continuous airway management and allows mask ventilation and positive pressure ventilation. It can be also inserted into a patient with spontaneous breathing, awake, or under anesthesia. This may be ideal for maintaining the patient’s airway during fiberoptic nasotracheal intubation. It is particularly useful in patients who require awake endotracheal intubation [46].

4) Nasotracheal intubation using a retromolar fiberscope: This method is generally referred to as “Bonfils” and uses a rigid fiberoptic endoscope that is useful in difficult airway management [47]. A tube of appropriate size was inserted into the nasal cavity and advanced until it reached the oropharynx. With the mandible pulled upward, the Bonfils endoscope was inserted into the oral cavity and advanced until the epiglottis and vocal cords were identified. After checking the position of the tracheal tube in the oropharynx, the tube was moved into the field of view of the Bonfils and inserted into the trachea. It requires a high level of skill and Magill forceps may be used. It may apply to patients with the immobilized cervical spine and significantly limited inter-incisor distance [47,48].

5) Use of lightwand (lighted stylet): A lightwand can be applied in the same way as in orotracheal intubation, but it should be inserted through the nasal cavity within the endotracheal tube. Therefore, it is difficult to apply this method with no flexibility. After the appropriate tube was inserted into the oropharynx, the lights in the operating room were dimmed, and a flexible lightwand was inserted into the tube by controlling the light rays appearing through the neck until it was seen directly above the cricothyroid membrane at the centerline of the neck. After that, the lightwand was fixed with one hand, and the tube was pushed with the other hand and inserted into the trachea.
The lightwand is supplied in various forms, but traumatic events such as airway damage can be prevented by selecting a flexible lightwand suitable for the patient’s condition and the skill level of the anesthesiologist [49,50].

6) Nasotracheal intubation using endotracheal tube introducer (bougie): One or two endotracheal tube introducers can be used when orotracheal intubation is performed. Nasotracheal intubation can also be performed by applying one or two introducers. When using dual introducers, a cuffed endotracheal tube is orally intubated into the trachea, and a cuffed tube with an appropriate size and shape for nasotracheal intubation is inserted into the nasal cavity before proceeding to the oropharynx. The endotracheal tube introducer was then inserted into the glottis through the nasal tube, and the laryngoscope and Magill forceps were used to access the trachea. After deflating the cuff of the orotracheal tube, the introducer was advanced into the trachea and placed in line with the orotracheal tube. After advancing the introducer already mounted with the nasotracheal tube into the trachea along the orotracheal tube using a laryngoscope and Magill forceps, the orotracheal tube was removed, and a nasotracheal tube was inserted. Nasotracheal intubation was completed by removing the introducer in the nasotracheal tube and checking the location of the tube. The endotracheal tube introducer enables nasal intubation using a video-laryngoscope with the Seldinger technique in children [51]. Alternatively, the orotracheal tube should be removed by splitting, and the introducer may be inserted into the endotracheal tube through the nose. The tube was inserted through the endotracheal tube, after which it was completely removed from the endotracheal tube. This method can be selected for patients who are expected to have difficulty in nasotracheal intubation, but it is not recommended as it is time-consuming and may require complicated maneuvers [52–54].

7. Airway care after nasotracheal intubation

After endotracheal intubation, the stable depth was checked and fixed. In most cases, the intubation depth is calculated based on orotracheal intubation, while a deeper depth is selected for nasotracheal intubation. Improper depth of endotracheal intubation may cause endobronchial intubation or damage to the vocal cords or bronchial tubes by the cuff or tube tip. The exact position of the endotracheal tube tip is the mid-trachea when the head of the patient is in a neutral position. It is selected considering the correlation with height, the sum of the distances from nares to the tragus, tragus to the angle of the mandible, and angle of the mandible to the sternal notch [55,56].

Several methods can be used to confirm the correct placement of the endotracheal tube. Usually, it is confirmed by auscultation of breathing sounds, but X-ray and fiberoptic bronchoscopy are applied as gold standards for confirmation of correct placement. In general, the mean distance from nares to the tip of endotracheal tube tip for nasotracheal intubation is 28.9 ± 1.3 cm in men and 26.6 ± 1.5 cm in women. In addition, palpation of the tube cuff in the suprasternal notch is an easy, fast, and cheap method [57,58].

In general, the exact position of the tube is 2–3 cm above the carina [48]. In addition to X-ray and fiberoptic bronchoscopy, ultrasonography can be used as a reliable method. Ultrasonography has the advantages of good mobility, safety, and good correlation compared to X-rays [55,59]. In adults, the length of endotracheal tube insertion varies depending on height. There is a method of presenting based on weight, but it is important to check the stable depth after insertion [60].

After endotracheal intubation, the depth of the tube was checked and fixed for stable management under anesthesia without interfering with the surgery. It may be possible to simply use adhesive tape or apply auxiliary devices while preventing the patient from being injured by pressure caused by fixing the tube. Recently, there has been a method of making it suitable for patients using a 3D printer [61].

8. Nasotracheal intubation in pediatric patients

In pediatric patients, there is also a method for determining the length of the endotracheal tube based on the internal diameter of the endotracheal tube. In other words, it is a method of measuring length by multiplying the tube size by three, but it is not an accurate method, resulting in malposition in 15–25% of cases [62]. In addition, the cuffed pediatric endotracheal tube (Microcuff® Pediatric Tracheal Tube, MPTT, Microcuff GmBH, Germany) used in children has a high volume with a low-pressure cuff. It is characterized by a small-sized cuff, low sealing cuff pressure, and a polyurethane tube with no Murphy’s eye. Confirmation of the endotracheal tube length using the depth marking of this tube allows safe mounting without risk of endobronchial intubation [63]. However, it should be noted that the black line may not be a depth marker depending on the tube manufacturer [64]. In children, the depth of the tube also changes depending on the head position. In other words, it should be remembered that the tube moves toward the carina during
flexion, away from the carina during extension and lateral rotation, resulting in malposition of the tube. It is important to maintain a neutral position, that is, a sniffing position [65,66].

Using a tube with a cuff requires attention to the cuff pressure. When the cuff pressure reaches 30 cmH₂O, the tracheal mucosal blood flow is compromised, and when the cuff pressure reaches 45 cmH₂O, the mucosal blood flow is completely obstructed [21]. It has been reported that tube lubrication with K-Y jelly (Johnson & Johnson, USA) inhibits the increase in cuff pressure in vitro when using a tube with a cuff under general anesthesia using N₂O. However, its clinical significance is limited [67]. The advantage of using an uncuffed tube in children is that a tube with a larger internal diameter can be used, thereby reducing airway resistance and work of breathing. However, leakage may occur because of incomplete sealing. In this case, leakage can be reduced by throat pack placement and mouth opening. The reason for the decrease in leakage when the mouth is open is that the mandible moves toward the larynx to decrease the thyromental distance, thereby physically compressing the soft tissue in between. This method improves sealing and reduces leakage [68]. Adequate endotracheal tube length can be predicted by using the equations for predicting the adequate tube depths in Japanese patients: (patient’s height / 10) – 3 + DM (distance between the distal edge of intubation guide mark and the tip, in cm) for oral intubation, and (patient’s height / 10) + 1 + DM for nasal intubation [19,69].

Instruments for nasotracheal intubation

1. Endotracheal tube
   1) Tube type
      (1) Standard endotracheal tube: This refers to the use of a conventional tracheal tube for orotracheal intubation. Standard endotracheal tubes that can be used for nasotracheal intubation can be classified into polyvinyl chloride, rubber, and polyurethane tubes, depending on the material, and armored tubes that emphasize flexibility. In nasotracheal intubation, care must be taken as the tube is hard and likely to damage the surrounding tissues, causing complications such as epistaxis. In some cases, the end of the tracheal tube is warmed to soften the end to reduce damage during insertion [70,71]. In addition, if the length of the tube is short and is inserted at an appropriate depth, the connection between the endotracheal tube and the breathing circuit is located at the entrance of the nasal cavity. Care should be taken to avoid damage to the nares and disconnection, affecting not only ventilation but also the surgical field of view. Unlike orotracheal intubation, a tube with a small diameter is chosen to pass through the nasal cavity, but it should not be excessively small [2–4]. Tubes without cuffs can be inserted smoothly, but to prevent air leakage, they are packed in the peri-cuff area for clinical application. In general, a nasal tube with a longer length and smaller diameter tends to be selected, thereby increasing the resistance to breathing [3–5].

      (2) RAE (Ring, Adair, Elwyn) endotracheal tube: The endotracheal tube for nasotracheal intubation is longer than that for orotracheal intubation and is bent upward or downward at the nasal entrance so that it can be fixed without obstructing the surgical field of view. It is more effective because it is longer and more flexible than a standard endotracheal tube.

      (3) Parker Flex-tip nasal endotracheal tube: Owing to the left-sided bevel and right tip orientation of a conventional tube, insertion through the right nostril during nasal passage is likely to cause turbinate damage, while insertion through the left nostril is likely to cause damage to the septum. On the other hand, a Parker Flex-tip tube is composed of a posterior bevel and an anterior tip so that the tip and bevel are not in contact with the turbinate and septum. In addition, the soft and flex tips are in contact with a wider area and pass smoothly along the curve of the nasopharynx. Therefore, it results in less nasal mucosal trauma and epistaxis and is suitable for nasotracheal intubation [72,73]. However, some argue that the softness of the tube tip is more important than the shape of the tube. In addition, the surgical procedure may be difficult because of vertical protrusion from the nostril. Another disadvantage is that the risk of airway obstruction may increase because of the high chance of tube kinking (Fig. 1) [73,74].

   2) Shape of the endotracheal tube tip
      A conventional tube with a Murphy eye is called a Murphy-tip, and a sharp-edged Murphy eye has a high probability of causing mucosal trauma in the process of passing through the nasal cavity. A Magill tip has no Murphy eye and has a shorter and blunter tip, which is less likely to cause nasal mucosal trauma [75].
2. Laryngoscope

The laryngoscope is an instrument that can directly visualize and identify the structures constituting the upper airway, which plays an important role in endotracheal intubation. A direct laryngoscope serves as the basic standard technique for endotracheal intubation. It guides the path for the endotracheal tube as it passes through the vocal cord and can be easily inserted into the airway by exposing the inside of the larynx during the process of securing the airway. Another method is to attempt endotracheal intubation indirectly. Some methods are gradually disappearing, while there are methods newly applied to clinical practice, such as methods using malleable or rigid optical stylets and methods using a rigid indirect laryngoscope (e.g., Bullard laryngoscope, TruView EVO₂, fiberoptic, and video-laryngoscope) [75].

1) Direct laryngoscope and blade

Recently, blades used with direct laryngoscopes have been supplied in various shapes and materials, including disposable and reusable ones, and it is possible to choose a blade of the size and length that suits the patient’s condition.

(1) Macintosh blade: The Macintosh blade provides a view of the larynx by mounting the tip of the blade on the vallecula and indirectly lifting the epiglottis. The base of the epiglottis is suspended in the hyoepiglottic ligament and hyoid bone. When the hyoepiglottic ligament is lifted in the distal direction, the epiglottis is elevated to visualize the glottic opening. The large flange of the Macintosh blade is advantageous for the displacement of the tongue, and the curved blade lifts the epiglottis, facilitating intubation [76].

(2) Miller blade: The Miller blade was placed under the epiglottis to visualize the laryngeal structures. Since it is a blade that exposes the glottic opening, it is useful for a large, floppy, and irregularly shaped epiglottis. The small spatula and flange make it particularly useful for patients with smaller displacement spaces. In other words, it is useful in children and patients with micrognathia, prominent upper incisors, and short mental-hyoid distance. Therefore, it provides a better view of the laryngeal structures [76].

(3) McCoy blade: The McCoy blade was developed in the early 1990s for difficult intubation in adult patients. It has an articulating distal tip to improve the lift of the epiglottis [76,77].

2) Indirect laryngoscope

Indirect laryngoscopes include optical stylets, rigid fiberoptic laryngoscopes, rigid video-laryngoscopes, and flexible fiberoptic laryngoscopes.

(1) Optical stylets: Optical stylets included the Shikani Seeing Stylet (Clarus Medical LLC, USA), Fiberlightview Shuttle (Anesthesia Medical Specialties, USA), video optical intubation stylet (Velpi AG, Switzerland), and Bonfils intubation fiberscope (Karl Storz Endoscopy, Germany). Compared to the malleable Shikani Seeing Stylet, Bonfils is a stylet modified by applying a fixed curve to the distal end of the initial rigid and straight design. Both types have good controllability and can be used to open the mouth enough to fit the endotracheal tube [76,77].

(2) Rigid fiberoptic laryngoscope: It includes the Bullard la-
The Bullard laryngoscope, introduced in 1988, enables intubation even in patients with limited mouth opening with a dedicated intubating stylet [76]. TruView EVO facilitates easy observation and operation of the laryngoscope with a digital camera mounted on the viewport. Rigid-type laryngoscopes are not widely used because they are not flexible and are less popular than video-laryngoscopes [76].

3. Rigid video-laryngoscopy: It includes Airtraq, GlideScope, Pentax Airway Scope, McGrath, CoPilot, and Storz C-MAC. The video-laryngoscope resembles a direct laryngoscope. A video chip was attached to show the laryngeal view. It shows the larynx better than the direct laryngoscope and is the first choice when difficult intubation is expected. However, it should be noted that providing a good laryngeal view does not always facilitate intubation [76–78]. The C-MAC has a blade similar to the shape of a Macintosh laryngoscope and requires a technique similar to that of a direct laryngoscope. The C-MAC video-laryngoscope is almost always used for difficult airway management. Alternatively, GlideScope, McGrath, and CoPilot have an angulated blade with a sharper curve [79]. The GlideScope has a high-resolution video camera on the laryngoscope blade, which varies in size from child to adult. The McGrath can be used by inserting a single-use blade with a view monitor placed on the handle with a disposable battery. The monitor can be tilted and swiveled to adjust the position of the view [77, 80]. The CoPilot has a C-shaped bougie port channel on the laryngoscope blade, and the endotracheal tube passes through the bougie, making it easy to mount the tube. This videolaryngoscope is excellent for teaching, as educators and trainees can share views at the same time. The view is limited in direct laryngoscopy because the distance between the glottis and the viewer only provides a view angle of 15–30°. The camera lens is near the tip of the laryngoscope with a view angle of 50–60° in the videolaryngoscope, allowing a better laryngeal view [76]. Lastly, Airtraq cannot be used because it has a reusable optic piece and is used in intubation by loading an endotracheal tube through a guide channel; however, the use of Airtraq (Airtraq NT) for nasotracheal intubation is considered possible [81].

4. Magill forceps

After insertion of the endotracheal tube through the nasal cavity, the provider safely holds the distal part of the endotracheal tube with the Magill forceps. The endotracheal tube is inserted into the larynx under the laryngoscope during nasotracheal intubation without trauma to the patient and without damaging the tube or cuff. Sufficient length is required with a good handle of the tube, and the handle should not interfere with the view, occupy minimal space, and should be held firmly [84].

There are several modified Magill forceps. The Boedeker forceps, which are curved intubating forceps, are designed to facilitate the removal of foreign bodies with the distal forceps well seen on the videolaryngoscope. The forceps are bent at two points for easy handling of the tube in the glottis, and the modified Magill forceps facilitate intubation into the cephalad larynx and the posterior angled trachea in children [85–87].

5. Endotracheal tube introducer (bougie)

This is not a common choice, but it may be chosen according to the preferences and skills of the anesthesiologist and the patient’s condition. In general, there should be at least two introducers for nasotracheal intubation. One introducer was inserted through the nasal cavity to be connected to the oropharynx, with another introducer inserted through the oral cavity to the bronchus. After nasotracheal intubation, both introducers can be removed through the endotracheal tube, but they must be flexible enough to reduce damage; therefore, material selection is important [88, 89].

Indications and contraindications for nasotracheal intubation

1. Indications for nasotracheal intubation

In oral and maxillofacial surgeries, such as intraoral or
mandibular surgeries, nasotracheal intubation has been chosen as the route of choice because it ensures a stable airway without disturbing the surgical field. It is a useful technique when orotracheal intubation is difficult, for example, trismus, previous radiation therapy, and oropharyngeal infection (Table 1) [3–9].

2. Contraindications for nasotracheal intubation

Nasotracheal intubation may result in complications or an increased risk of injury, such as penetrating trauma of the frontal lobe through the cribriform plate as the endotracheal tube is inserted due to basilar skull fracture during nasotracheal intubation [2–5]. In patients with clotting factor deficiency, severe epistaxis may be caused by mucosal trauma during tube progression through the nasal cavity [2–6]. Patients should be thoroughly checked for antiplatelet medication, anticoagulation medication, or hereditary telangiectasia. Care should be taken in patients with cardiac valvular abnormalities or prosthetic valves, as there is a high risk of tube-induced bacteremia. In addition, blind nasotracheal intubation may be contraindicated in patients with upper airway foreign bodies or severe facial trauma (Table 2) [2–5,44].

Complications

1. Types of complications

1) Epistaxis: Epistaxis is the most common complication of nasal mucosal trauma. It is mainly caused by damage to Kisselbach's plexus in Little's area, located in the anterior region of the nasal septum. This may be caused by the large size of the endotracheal tube, excessive force, repeated attempts, and inappropriate vasoconstriction. During severe epistaxis, there is a possibility of pulmonary aspiration, and it is necessary to control bleeding by packing the posterior nasal space [5–7].

2) Bacteremia: When performing the procedure around the oral cavity under general anesthesia, the incidence of bacteremia is high. This may be caused by the invasion of the nasal flora into the highly vascularized trachea. Thus, prophylactic antibiotic administration should be considered in patients with prosthetic cardiac valves. The causative bacteria include alpha-hemolytic Streptococcus and Corynebacterium species [2–4].

3) Obstruction of the nasotracheal tube: Obstruction may occur due to avulsion of the nasal polyp or inferior turbinate, tooth, and blood clot; obstruction of the main bronchus may cause serious ventilatory disturbance [2–6].

4) Retropharyngeal perforation: Laceration is caused by dissection of the retropharyngeal mucosa, which may lead to perforation in severe cases. If resistance occurs in the tube passage or if a breathing sound is not heard, it should be recognized that the tube is already located on the pharyngeal wall. If there is a possibility of complications, broad-spectrum antibiotics should be administered to reduce the risk of infection [4–6].

5) Perforation of pyriform fossa: Pyriform fossa perforation can lead to subcutaneous and mediastinal emphysema. Therefore, care should be taken to monitor the condition of critically ill patients [2–4].

6) Sinusitis: Factors that can cause sinusitis include the presence of foreign bodies in the nasal cavity, retention of secretions, bacterial colonization, immunosuppression, supine position, and variation in the size of sinus ostium. It can be diagnosed using sinus needle aspiration or culture [4–6].

7) Pneumonia: Pneumonia can be caused by various factors, and its prevalence is higher in patients who undergo nasotracheal intubation than in those who undergo orotracheal intubation [3–5].

8) Sepsis: Pneumonia, sinusitis, and sepsis are the most frequent late complications. Sepsis can be diagnosed based on positive findings and clinical evidence of infection in

Table 1. Indications of Nasotracheal Intubation

<table>
<thead>
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<th>Indications of Nasotracheal Intubation</th>
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<tbody>
<tr>
<td>Intranasal and oropharyngeal surgery</td>
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<tr>
<td>Mandible surgery</td>
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<td>Maxillofacial surgery</td>
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<td>Limited mouth opening due to trismus</td>
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<tr>
<td>Dental surgery</td>
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<td>Rigid laryngoscopy and microlaryngeal surgery</td>
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<td>Cervical spine instability or severe degenerative cervical spine disease</td>
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Table 2. Contraindications of Nasotracheal Intubation

<table>
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<tr>
<th>Contraindications of Nasotracheal Intubation</th>
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<tr>
<td>Basilar skull fractures combined with or without cerebrospinal fluid leakage</td>
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<td>Coagulopathy</td>
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<td>Epiglottitis</td>
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<tr>
<td>Nasal foreign bodies</td>
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<tr>
<td>Nasal polyp</td>
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<tr>
<td>Frequent episodes of epistaxis</td>
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<tr>
<td>Prosthetic heart valves</td>
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<tr>
<td>Nasal bone fracture</td>
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<tr>
<td>Patients with facial trauma such as facial bone fracture</td>
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blood cultures [3–5].
9) Other complications: Inadvertent intracranial placement of the nasotracheal tube can cause fracture of the cribiform plate due to damage to the middle turbinate, anosmia due to olfactory nerve injury, CSF rhinorrhea, meningitis, hemiparesis, and blindness due to brain damage in severe cases [2–7]. It may also result in inferior turbinate ulceration, laryngitis, vocal cord paralysis, otitis media due to obstruction of the Eustachian tube by a nasotracheal tube, and necrosis of the nasal ala. With repeated insertion into the esophagus, especially in the presence of a malignancy or inflammation in the esophageal wall, esophageal perforation may be induced (Table 3) [2–6,44].

2. Risk factors for complications
In the preoperative examination, the medical history and patient’s conditions related to risk factors that may cause complications from nasotracheal intubation should be checked (Table 4) [2–6].

Prevention
The methods that can be applied to prevent complications caused by nasotracheal intubation are listed below.
1. After nasotracheal intubation, several methods have been used to prevent and reduce the risk of epistaxis, which is the most common complication. One of the methods is to use topical vasoconstrictors such as epinephrine, phenylephrine, xylometazoline, and oxymetazoline. However, as these may cause life-threatening complications such as arrhythmia, myocardial infarction, and cardiac arrest, care should be taken when choosing the drug and dosage [90].
2. It has been reported that the same preventive effect for epistaxis as a thermosoftened tube could be obtained by inserting an esophageal stethoscope into the endotracheal tube, ballooning the stethoscope, and obstructing the tip of the tube with the tip of the stethoscope [90]. Similarly, it has been reported that the combination of tube softening and red-rubber catheter-guided intubation reduces epistaxis [91,92].
3. Nasotracheal intubation under a curve-tipped suction catheter guide and intubation using a “Bubble-tip” (Air-guide®) tracheal tube system are also introduced as methods to reduce epistaxis [91–93].
4. Since the Parker Flex-Tip tube has a posteriorly oriented bevel and slides along the posterior wall, it has been reported to reduce the epithelial stripping of the turbinate and septum, and the soft flex tip contacts the mucosa on many surfaces to reduce tissue pressure [72,73].
5. Because lower pathway intubation of the nose decreases the trauma and epistaxis of the middle turbinate, tube advancement between the floor of the nose and inferior turbinate is a better approach for the prevention of trauma [2–9].
6. Reinforced tubes are slightly larger in external diameter than relatively firm and inflexible preformed tubes, but their flexibility allows them to easily enter narrow pathways, resulting in easier tube passage through the lower pathway [8,9].
7. The Murphy tip endotracheal tube can induce trauma of the nasal mucosa as the sharp-edged Murphy eye passes through the nasal cavity. However, if there is no murphy eye, the shorter Magill-tip endotracheal tube has a blunt tip, causing a small impaction of the nasal mucosa, thereby reducing trauma [75].

Table 3. Complications of Nasotracheal Intubation

<table>
<thead>
<tr>
<th>Epistaxis</th>
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<tr>
<td>Bacteremia</td>
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<td>Obstruction of the nasotracheal tube</td>
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<tr>
<td>Retropharyngeal perforation</td>
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<tr>
<td>Perforation of pyriform fossa</td>
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<tr>
<td>Sinusitis</td>
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<tr>
<td>Pneumonia</td>
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<tr>
<td>Sepsis</td>
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<tr>
<td>Other complications</td>
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<tr>
<td>CSF rhinorrhea due to the intracranial placement of the nasotracheal tube, brain damage, meningitis, hemiparesis, blindness, fracture of the cribiform plate, olfactory nerve injury and anosmia, inferior turbinate ulceration, laryngitis, vocal cord paralysis, otitis media caused by Eustachian tube obstruction, necrosis of nasal ala, esophagus intubation, esophageal perforation</td>
</tr>
</tbody>
</table>

Table 4. Risk Factors for Complications

| Abnormal anatomy: septal deviation, etc. |
| Pre-existing medical condition:         |
| Gastroesophageal reflux disorder,      |
| Coagulopathy or antiplatelet medication |
| Large tube size selection               |
| Cuff pressure too high                  |
| Presence of nasogastric tube            |
| Excessive force during intubation       |
| Repeated tube insertion                 |
| Swelling or infection of the surrounding organs, such as sinusitis |
8. The use of a silicone tube with a soft and round tip, although expensive, can reduce epistaxis or nasal complications. Methods to prevent and reduce the complications of nasotracheal intubation include the use of mechanical dilation, sterile lubrication, water-soluble jelly, tubes with smaller diameters, gentle tubes, and softened tube tips by warming up [29, 75, 90].

9. In patients with head and neck tumors, it may be difficult to maintain and manage airways due to anatomical and physiological changes, as well as radiation therapy and chemotherapy [22]. It should be approached in consideration of the fact that tumors may cause difficulties in airway management due to abnormalities such as receding jaw, restricted mouth opening, and neck movement abnormalities. Depending on the size and location of the tumor, complications such as obstruction and bleeding in the nasal cavity, through which the tracheal tube passes, and the selection and placement of the laryngoscope and blade may affect the surgical field of vision [94, 95].

10. The restriction of neck movement, especially neck stiffness, is often accompanied by intubation difficulties due to insufficient neck extension due to contracture caused by radiation therapy. Adequate preoperative judgment, mask ventilation, and endotracheal intubation during surgery should be prepared to prevent complications and to reduce airway-related morbidity, along with a reliable plan to ensure safe airway management [94, 95].

CONCLUSION

Nasotracheal intubation is a basic procedure that replaces orotracheal intubation in oral or maxillofacial surgery and intensive care management. By learning and acquiring techniques for direct laryngoscopy, video-laryngoscopy, use of Magill forceps, and selection of an endotracheal tube for nasotracheal intubation, which is being applied as a basic method for all airway management from blind nasotracheal intubation, it will be possible to safely manage the airway. This will also allow quick coping with unexpected difficulties in intubation, securing the view of an appropriate surgical field, and preventing side effects and complications from the insertion process.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.
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Comparison of the effects of normal and low blood pressure regulation on the optic nerve sheath diameter in robot assisted laparoscopic radical prostatectomy

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Background: Robot-assisted laparoscopic radical prostatectomy is an advanced and popular surgical technique. However, increased intracranial pressure which is caused by CO₂ pneumoperitoneum and Trendelenburg position is the main cerebrovascular effect. Measurement of optic nerve sheath diameter using ocular ultrasound is a noninvasive and reliable method for the assessment of intracranial pressure. The primary endpoint of this study was to identify whether low blood pressure regulation has any benefit in attenuating an increase of optic nerve sheath diameter during robot-assisted laparoscopic radical prostatectomy.

Methods: Optic nerve sheath diameter and cerebral oxygen saturation were measured at baseline (supine position), one and two hours after pneumoperitoneum and Trendelenburg position respectively, and after return to supine position in normal (n = 27) and low blood pressure groups (n = 24).

Results: Mean optic nerve sheath diameter values measured at one and two hours after pneumoperitoneum and Trendelenburg position were significantly increased compared to the baseline value (P < 0.001 in normal blood pressure group; P = 0.003 in low blood pressure group). However, the mean optic nerve sheath diameter and cerebral oxygen saturation measured at any of the time points as well as degrees of change between the two groups did not show any significant changes. The peak values of optic nerve sheath diameter in normal and low blood pressure groups demonstrated 14.9% and 9.2% increases, respectively.

Conclusions: Low blood pressure group demonstrated an effect in maintaining an increase of optic nerve sheath diameter less than 10% during CO₂ pneumoperitoneum and Trendelenburg position.

Keywords: Blood pressure; Cerebral oxygen saturation; Optic nerve sheath diameter; Pneumoperitoneum; Trendelenburg position.
INTRODUCTION

Robot-assisted laparoscopic radical prostatectomy (RAL-RP) is an advanced and popular surgical technique with benefits of reduced intraoperative bleeding, less postoperative pain, good surgical field and shorter hospital stay [1,2]. However, RALRP requires CO₂ pneumoperitoneum with steep Trendelenburg position to enhance the clarity of the surgical field, which causes unwanted hemodynamic, respiratory, and cerebrovascular events.

Among such adverse events, increased intracranial pressure (ICP) which is caused by CO₂ pneumoperitoneum and Trendelenburg position either independently or in conjunction is the main cerebrovascular effect [1,3–5]. Early diagnosis and proper management of increased ICP play an essential role in preventing further brain damage. In spite of the importance of increased ICP during surgery, it is rarely monitored intraoperatively due to the invasiveness of the ICP measurement. Direct measurement of ICP involves measuring pressure in the ventricle or the brain parenchyma directly [6]. However, such an invasive method makes the popular use of ICP monitoring difficult. An alternative non-invasive method for ICP assessment is using optic nerve sheath diameter (ONSD) measurement by ultrasonography [6–8].

Measurement of ONSD using ocular ultrasound is a non-invasive and reliable method for the assessment of ICP. Numerous studies have proven that ONSD measured by ocular ultrasound correlates well with the degree of ICP changes [9–13]. Also, this measurement technique has shown excellent intra-observer and inter-observer reproducibility (0.25–0.3 mm) [14,15].

Previous study which investigated the elevation of ICP during RALRP suggested that postoperative ONSD changes were significantly associated with regulation of mean arterial pressure (MAP) [2]. According to this study, a 10 mmHg increase in MAP resulted in a 0.023 mm increase in postoperative ONSD. However, only a small number of participants were studied to identify this correlation between MAP and ONSD. Moreover, this study did not demonstrate any range or degree of MAP regulation during the entire study period [2].

Cerebral circulation can be assessed by measurement of regional cerebral oxygen saturation (rSO₂) values using near infrared spectroscopy. Previous study which evaluated changes in rSO₂ during RALRP demonstrated that changes of rSO₂ correlated with MAP and PaCO₂ [16].

The purpose of this study was to identify whether low MAP regulation has any benefit in attenuating an increase in ONSD. The primary endpoint of this study was to compare the differences in ONSD changes during surgery between the normal and hypotensive groups. The secondary endpoint of this study was to compare the changes of ONSD and rSO₂ when MAP was tightly regulated between pressure ranges corresponding to normal (95–105 mmHg) and low (65–75 mmHg) during RALRP.

MATERIALS AND METHODS

Subjects

This prospective and randomized study was approved by the Institutional Review Board (no. 19-07-049) of our institution. Written and verbal information about the potential benefits and risks of the study were provided. All participants provided written informed consent. This study was registered before patient enrollment at clinicalTrials.gov (NCT04339244, Date of registration: 6th-April-2020).

Patients with American Society of Anesthesiologists class I to II who were scheduled for an elective RALRP using the da Vinci Si robot system (Intuitive Surgical Inc., USA) between April 2020 and September 2020 were included in this study. Patients with preexisting ophthalmic and cerebrovascular disease or previous history of brain or ophthalmic surgery were excluded. Patients with a previous history of uncontrolled hypertension in spite of using antihypertensive medication were excluded.

Anesthetic management

The participants arrived in the operating room without premedication. Electrocardiography, pulse oximetry and noninvasive blood pressure monitoring were applied. General anesthesia was induced with propofol 1.5 mg/kg, rocuronium bromide 0.9 mg/kg and remifentanil 1 μg/kg. After successful tracheal intubation, mechanical ventilation of volume control mode was performed with a tidal volume of 8–10 ml/kg and an adjusted respiratory rate to maintain an end-tidal CO₂ (EtCO₂) of 30 to 35 mmHg during surgery.

For the purpose of continuous arterial blood pressure monitoring and sampling for arterial blood gas analysis, radial artery cannulation was performed. Continuous cardiac output was measured directly from this arterial line (FloTracTM, Edward Life Science, USA). Anesthesia was maintained with 1 to 1.5 minimum alveolar concentration of sevo-
flurane in 60% oxygen/air and remifentanil 0.05 to 0.3 μg/kg/min. An adequate anesthetic depth was maintained using a SedLine monitor (SedLine™, Masimo Corp., USA) and a range of 25–50 patient state index was targeted during surgery. An rSO2 was assessed during surgery. Cerebral oximeter sensors were applied 2 cm above the eyebrow on the left and right sides of the forehead bilaterally before induction of anesthesia. The value of rSO2 was continuously monitored using O3 regional oximetry (Root®, Masimo Corp., USA).

CO2 was infused with an intra-abdominal pressure of 15–20 mmHg using the da Vinci Si robot system while the patient’s position was supine. Trendelenburg position was applied to 30-degrees. During the period of CO2 pneumoperitoneum, minute ventilation was regulated to maintain an EtCO2 of 30 to 35 mmHg by adjusting the respiratory rate.

**Group allocation**

This study focused on measuring the ONSD using ocular ultrasonography under different MAP regulation. Participants in the normal and low blood pressure groups were randomly assigned to be controlled to either a MAP of 95–105 mmHg (normal blood pressure group) and 65–75 mmHg (low blood pressure group) using a computer-generated randomization table. MAP was mainly regulated using the target concentration of remifentanil. In the low blood pressure group, MAP was regulated between 65–75 mmHg using remifentanil at 0.2 to 0.3 μg/kg/min. In normal blood pressure group, MAP was regulated within 95–105 mmHg using remifentanil 0.05 to 0.2 μg/kg/min. Strict regulation of MAP in normal and low blood pressure groups was targeted. However, transient MAP changes either above or below assigned pressure ranges for less than one minute were allowed without using any blood pressure regulating medications.

**Measurement of ONSD**

A single trained investigator with more than 200 scans of ONSD measurement and fully experienced with previous studies [1,17] conducted this ultrasonographic measurement. This investigator was blinded to the group assignment. Transorbital sonography using a hockey stick probe (Logiq S8, GE Healthcare, USA) was performed to measure ONSD. The power output was reduced (mechanical index, 0.2; thermal index, 0) to minimize the risk of ultrasound-induced eye injury. Participants were asked to close their eyes and a sterile gel was applied on each closed upper eye-lid. The hockey stick probe was placed gently to minimize the exerted pressure on eyeball. The probe was moved using heel-toe method to capture the best axial image of the orbit in the plane of the optic nerve. The depth parameter was controlled within 3.0–4.0 cm. ONSD was measured 3 mm posterior to the optic nerve head (Fig. 1) [13,17,18]. ONSD images were obtained when the postural effects were stabilized with no further external stimuli.

Each ONSD was measured serially in each eye at the following time points: awake state in supine position before anesthesia induction (baseline, T0), one hour after 30-degree Trendelenburg position with CO2 pneumoperitoneum (T1), two hours after 30-degree Trendelenburg position with CO2 pneumoperitoneum (T2), and 10 min after returning to supine position without CO2 pneumoperitoneum at the end of RALRP (T3).

*Fig. 1. Measurement of optic nerve sheath diameter by ultrasonography. Axial images of the orbit were acquired in the plane of the optic nerve. Optic nerve sheath diameters were measured 3 mm posterior to the optic nerve head (A–B).*
At each time point, to obtain more reliable value of ONSD, this measurement was performed twice on the right and twice on the left sides of the optic nerve, respectively. Therefore, the average of the four values was considered to be the final ONSD at each time point. If the measured ONSD was more than 5.5 mm which was the cut-off point used in a previous study, such patients were considered to have increased ICP [12].

The ONSD, rSO$_2$, heart rate, mean arterial pressure and cardiac output were examined from T0 to T3. The parameters regarding respiratory mechanics and arterial blood gas analysis were examined from T1 to T3.

In addition, the Trendelenburg and pneumoperitoneum time, operation and anesthesia time, intraoperative blood loss, and volumes of administered fluid were recorded.

**Statistical analysis**

This study was designed to identify whether there would be any differences in ONSD according to MAP regulation. Previous study demonstrated that a difference in ONSD $>0.5$ mm (10% of mean ONSD in asymptomatic normal adults [mean ONSD 4.9 mm]) would be clinically relevant [12]. Given a 5% two-tailed significance level, a power of 80% and a dropout rate of 15%, 24 patients per group were required to detect a mean difference of 0.5 mm between ONSD in normal and low blood pressure groups.

All variables were reported as mean ± SD. Patient characteristics and operative data were compared by unpaired t-test. Except for ONSD and rSO$_2$ intergroup comparisons for repeated measures, including hemodynamic and respiratory parameters were performed by unpaired t-test with Bonferroni correction. Repeated ONSD and rSO$_2$ measurements were analyzed by linear mixed models for random and fixed effects between the two groups. The Shapiro–Wilk test was applied before performing the LMM and the variables were distributed normally.

Intergroup comparison of changes in ONSD over time was performed by group-by-time interaction. All statistical values were two-tailed, and P values < 0.05 were considered to be statistically significant. Statistical evaluations were performed using SPSS version 22.0 (IBM Corp., USA).

**RESULTS**

Eligibility was assessed in 58 patients and 51 of these patients completed this study without dropout. Two patients refused to participate in this study and five patients were excluded due to a failure of proper MAP regulation to the assigned group. Therefore, final enrolled participants were 51 patients (Fig. 1). Patient characteristics and intraoperative data are described in Table 1.

Mean blood pressure of the low blood pressure group was significantly lower than the normal blood pressure group from T1 to T3 (Table 2, P = 0.001). Respiratory mechanics and arterial blood gas analysis did not show any significant changes between normal and low blood pressure groups (Table 3).

Both normal and low blood pressure groups showed significant increases of ONSD according to time. Mean ONSD values measured at T1 and T2 significantly increased compared to the baseline value at T0 (Table 4, P < 0.001 in normal blood pressure group; P = 0.003 in low blood pressure group). However, the mean ONSD values measured at any of the time points and degrees of changes (T1-T0, T2-T0, and T3-T0) between two groups did not show any significant changes. Normal and low blood pressure groups showed peak value of ONSD at T2 and T1, respectively (Table 4, Fig. 2). The peak value of ONSD in normal and low blood pressure groups demonstrated 14.9% (T2 vs. T0) and 9.2% (T1 vs. T0)

| Table 1. Patient Demographics and Intraoperative Data Assigned to Normal Blood Pressure or Low Blood Pressure Group during Robot-assisted Laparoscopic Radical Prostatectomy |
|-----------------|----------------|----------------|
| Variable                    | Normal blood pressure group (n = 27) | Low blood pressure group (n = 24) | P value |
| Age (yr)                    | 68.3 ± 6.1 | 68.8 ± 6.3 | 0.782 |
| BMI (kg/m$^2$)              | 25.5 ± 2.7 | 25.5 ± 2.6 | 0.951 |
| Trendelenburg and pneumoperitoneum time (min) | 127.9 ± 21.7 | 138.6 ± 33.4 | 0.182 |
| Operation time (min)        | 167.4 ± 26.7 | 174.2 ± 32.5 | 0.423 |
| Anesthesia time (min)       | 214.8 ± 28.3 | 217.9 ± 37.2 | 0.741 |
| Intraoperative blood loss (ml) | 244.4 ± 95.4 | 237.5 ± 90.0 | 0.792 |
| Intraoperative fluid intake (ml) | 1,192.6 ± 277.2 | 1,354.2 ± 321.7 | 0.063 |

Values are presented as mean ± SD. BMI: body mass index.
### Table 2. Hemodynamic Parameters during Robot-assisted Laparoscopic Radical Prostatectomy in Normal Blood Pressure and Low Blood Pressure Groups

<table>
<thead>
<tr>
<th>Hemodynamic parameters</th>
<th>Normal blood pressure group (n = 27)</th>
<th>Low blood pressure group (n = 24)</th>
<th>Adjusted P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>T0 67.7 ± 16.6</td>
<td>69.7 ± 9.8</td>
<td>0.592</td>
</tr>
<tr>
<td></td>
<td>T1 65.1 ± 12.5</td>
<td>63.9 ± 9.8</td>
<td>0.701</td>
</tr>
<tr>
<td></td>
<td>T2 66.5 ± 11.2</td>
<td>63.7 ± 8.7</td>
<td>0.442</td>
</tr>
<tr>
<td></td>
<td>T3 69.7 ± 11.7</td>
<td>64.5 ± 10.0</td>
<td>0.103</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>T0 93.6 ± 9.4</td>
<td>93.3 ± 9.6</td>
<td>0.974</td>
</tr>
<tr>
<td></td>
<td>T1 97.5 ± 5.2</td>
<td>69.0 ± 8.0</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>T2 97.0 ± 8.7</td>
<td>68.5 ± 9.4</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>T3 95.1 ± 4.8</td>
<td>67.6 ± 8.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>T0 5.1 ± 1.3</td>
<td>4.8 ± 0.8</td>
<td>0.362</td>
</tr>
<tr>
<td></td>
<td>T1 4.2 ± 1.4</td>
<td>3.6 ± 0.7</td>
<td>0.101</td>
</tr>
<tr>
<td></td>
<td>T2 4.1 ± 1.3</td>
<td>3.8 ± 0.7</td>
<td>0.432</td>
</tr>
<tr>
<td></td>
<td>T3 5.2 ± 1.5</td>
<td>4.7 ± 1.1</td>
<td>0.211</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. Adjusted P value indicates the Bonferroni-corrected P value. T0: supine position before anesthesia induction (baseline); T1, 1 h after 30-degree Trendelenburg position with CO2 pneumoperitoneum; T2, 2 h after 30-degree Trendelenburg position with CO2 pneumoperitoneum; T3, 10 min after returning to supine position without CO2 pneumoperitoneum at the end of surgery.

### Table 3. Respiratory Mechanics and Arterial Blood Gas Analysis during Robot-assisted Laparoscopic Radical Prostatectomy in Normal Blood Pressure and Low Blood Pressure Groups

<table>
<thead>
<tr>
<th>Respiratory parameters</th>
<th>Normal blood pressure group (n = 27)</th>
<th>Low blood pressure group (n = 24)</th>
<th>Adjusted P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak inspiratory pressure (cmH2O)</td>
<td>T1 23.3 ± 4.9</td>
<td>24.1 ± 3.5</td>
<td>0.512</td>
</tr>
<tr>
<td></td>
<td>T2 23.5 ± 3.8</td>
<td>24.1 ± 3.8</td>
<td>0.591</td>
</tr>
<tr>
<td></td>
<td>T3 14.7 ± 5.0</td>
<td>13.7 ± 1.9</td>
<td>0.373</td>
</tr>
<tr>
<td>Respiratory rate (beats/min)</td>
<td>T1 13.6 ± 1.4</td>
<td>13.5 ± 1.6</td>
<td>0.762</td>
</tr>
<tr>
<td></td>
<td>T2 14.6 ± 1.6</td>
<td>14.1 ± 2.0</td>
<td>0.261</td>
</tr>
<tr>
<td></td>
<td>T3 13.8 ± 1.7</td>
<td>14.1 ± 2.4</td>
<td>0.602</td>
</tr>
<tr>
<td>End tidal CO2 (mmHg)</td>
<td>T1 33.4 ± 4.1</td>
<td>32.9 ± 3.4</td>
<td>0.593</td>
</tr>
<tr>
<td></td>
<td>T2 34.6 ± 4.3</td>
<td>33.8 ± 4.5</td>
<td>0.524</td>
</tr>
<tr>
<td></td>
<td>T3 36 ± 4.5</td>
<td>36 ± 5.8</td>
<td>0.992</td>
</tr>
<tr>
<td>End tidal sevoflurane (%)</td>
<td>T1 1.8 ± 0.3</td>
<td>1.9 ± 0.5</td>
<td>0.991</td>
</tr>
<tr>
<td></td>
<td>T2 2.1 ± 0.5</td>
<td>2.2 ± 0.2</td>
<td>0.991</td>
</tr>
<tr>
<td></td>
<td>T3 2.3 ± 0.2</td>
<td>2.2 ± 0.2</td>
<td>0.992</td>
</tr>
<tr>
<td>PaCO2 (mmHg)</td>
<td>T1 41.1 ± 4.8</td>
<td>41.6 ± 3.8</td>
<td>0.992</td>
</tr>
<tr>
<td></td>
<td>T2 44.6 ± 4.9</td>
<td>42.9 ± 5.5</td>
<td>0.561</td>
</tr>
<tr>
<td></td>
<td>T3 43.2 ± 4.2</td>
<td>44.8 ± 8.1</td>
<td>0.361</td>
</tr>
<tr>
<td>PaO2 (mmHg)</td>
<td>T1 165.0 ± 22.5</td>
<td>165.6 ± 18.1</td>
<td>0.991</td>
</tr>
<tr>
<td></td>
<td>T2 182.6 ± 32.1</td>
<td>182.7 ± 28.5</td>
<td>0.992</td>
</tr>
<tr>
<td></td>
<td>T3 186.0 ± 28.5</td>
<td>186.1 ± 34.1</td>
<td>0.994</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. Adjusted P value indicates the Bonferroni-corrected P value. T0: supine position before anesthesia induction (baseline); T1, 1 h after 30-degree Trendelenburg position with CO2 pneumoperitoneum; T2, 2 h after 30-degree Trendelenburg position with CO2 pneumoperitoneum; T3, 10 min after returning to supine position without CO2 pneumoperitoneum at the end of surgery.
increases, respectively. Twenty four patients (24/27, 88.8%) in the normal blood pressure group and 16 patients (16/24, 66.6%) in the low blood pressure group showed a value of ONSD above 5.5 mm (P = 0.05; the cutoff value for prediction of increased ICP) [12], and these patients did not experience a decrease of rSO2 or any neurologic complication.

The mean rSO2 values of the low blood pressure group showed higher values compared to normal blood pressure group from T0 to T3. However, this difference did not show any significant changes (Table 5, Fig. 3). Neurologic complications were not observed in any of the enrolled patients during the postoperative period in both groups.

**DISCUSSION**

The effect of CO2 pneumoperitoneum and steep Trendelenburg position during RALRP on ICP warrants a careful consideration. In this study, an increase in ONSD of more
than 0.5 mm, which represents a 10.0% increase compared to supine position without pneumoperitoneum, was considered to be the result of increased intracranial pressure [12]. The results of our study demonstrated that an increase of ONSD of 14.9% was observed during CO₂ pneumoperitoneum and Trendelenburg position in the normal blood pressure group, while a 9.2% increase was seen in the low blood pressure group. In addition, the number of patients who showed an increase of ONSD above 10% was higher in the normal blood pressure group compared to the low blood pressure group. Mean values of ONSD and rSO₂ during T0 to T3 did not show any significant difference between the two groups. If we consider an increase of ONSD more than 10% predicts an increased ICP during CO₂ pneumoperitoneum and Trendelenburg position, the normal blood pressure group shows a higher probability of increased ICP than the low blood pressure group. In this study, we used an ONSD value of 5.5 mm as the cutoff for prediction of increased ICP although other study suggested it should be 5.8 mm [11]. Since ONSD values differ according to ethnicity [19], the results obtained from a Caucasian population may not accurately reflect the association between increased ICP and ONSD in the Korean population. Therefore, we used the cutoff value of 5.5 mm as it was established among the Korean population [12].

ONSD increased due to steep Trendelenburg position and CO₂ pneumoperitoneum during RALRP. The dural sheath of the optic nerve is in close contact with the CSF in the intra-

### Table 5. Regional Cerebral Oxygen Saturation (rSO₂) during Robot-assisted Laparoscopic Radical Prostatectomy in Normal Blood Pressure and Low Blood Pressure Groups

<table>
<thead>
<tr>
<th>Regional cerebral oxygen saturation</th>
<th>Normal blood pressure group (n = 27)</th>
<th>Low blood pressure group (n = 24)</th>
<th>Adjusted P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rSO₂ (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>64.5 ± 5.3</td>
<td>65.8 ± 5.2</td>
<td>0.592</td>
</tr>
<tr>
<td>T1</td>
<td>66.7 ± 6.8</td>
<td>67.5 ± 4.9</td>
<td>0.901</td>
</tr>
<tr>
<td>T2</td>
<td>66.2 ± 5.9</td>
<td>68.8 ± 4.8</td>
<td>0.152</td>
</tr>
<tr>
<td>T3</td>
<td>67.3 ± 5.6</td>
<td>69.0 ± 5.4</td>
<td>0.564</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. Adjusted P value indicates the Bonferroni-corrected P value. T0, supine position before anesthesia induction (baseline); T1, 1 h after 30-degree Trendelenburg position with CO₂ pneumoperitoneum; T2, 2 h after 30-degree Trendelenburg position with CO₂ pneumoperitoneum; T3, 10 min after returning to supine position without CO₂ pneumoperitoneum at the end of surgery.

**Fig. 3.** Changes in optic nerve sheath diameter (A) and regional cerebral oxygen saturation (B) (rSO₂) in normal (filled circle) and low blood pressure groups (open circle). Data are mean with SD. T0, supine position before anesthesia induction (baseline); T1, 1 h after 30-degree Trendelenburg position with CO₂ pneumoperitoneum; T2, 2 h after 30-degree Trendelenburg position with CO₂ pneumoperitoneum; T3, 10 min after returning to supine position without CO₂ pneumoperitoneum at the end of surgery.
cranial subarachnoid space. Hence, any increase or decrease of ICP is directly transmitted to the CSF in the optic nerve sheath. The subarachnoid space surrounding the optic nerve sheath has an elastic trabecular structure [8,11,14]. It is most distensible 3 mm behind the papilla in the globe. Due to such distensibility, the optic nerve sheath inflates within a few minutes of exposure to increased ICP [1,7,14,17]. The Trendelenburg position has an effect to produce a moderate increase in ICP as seen with intracranial monitoring. CO2 pneumoperitoneum causes an increased intra-abdominal pressure. Such increases in intra-abdominal pressure can impair CSF drainage with resultant elevation of ICP [20]. In conjunction with increased intra-abdominal pressure, the elevated content of arterial CO2 during CO2 pneumoperitoneum increases the cerebral blood flow. As a result, ICP is expected to increase [1,3]. In this study, values of PaCO2 analyzed after pneumoperitoneum showed a tendency towards an increase. Hence, the increased PaCO2 might partially contribute to the increased ICP, although EtCO2 was near to normocapnia after adjusting for the respiratory rate.

The cerebral perfusion pressure (CPP) is known as MAP minus central venous pressure or ICP. If this equation was entirely true, ICP would equal to MAP-CPP implying no venous involvement [21]. Therefore, we can assume that if CPP is constant, the low blood pressure group will have lower ICP than the normal blood pressure group. However, ICP has a dynamic component which is affected by the brain, intracranial blood flow, and CSF. The average male intracranial volume including brain and CSF is around 1,473 ml and the brain receives blood flow approximately 14% of cardiac output (700 ml/min). At any moment in time, the intracranial blood volume is 100–130 ml. Therefore, brain, blood flow, and CSF should be considered during regulation of ICP [20,21].

ICP is regulated by arterial and venous influence. Previous study suggested that vena caval pressure can reflect CSF pressure due to the lack of valves in the cranio-vertebral venous system, and retinal venous distension could reflect intracranial venous pressure. ICP is affected by changes in vascular pressure especially with the greater importance of the venous system. Specifically, increasing central venous pressure results in increasing ICP when compliance is lost [1,16,20,21]. We assume that the effect of an attenuation in increase of ONSD in the low blood pressure group is related to lower intracranial vascular pressure compared to the normal blood pressure group.

Cerebral oxygenation can be monitored by rSO2 and it reflects cerebral perfusion. rSO2 is comprised of 25% arterial and 75% venous blood according to the manufacturer. Cerebral blood volume changes with variation in PaCO2 [16]. Carbon dioxide insufflated abdominally during pneumoperitoneum is absorbed into the systemic circulation and is exhaled with ventilation. We could observe a slight increase in PaCO2 during time points of T1 and T2 although it did not exceed 45 mmHg. In addition to this increase of PaCO2, the steep head down tilt position is known to cause an increase in cerebral blood volume. Previous study measured cerebral blood volume using near-infrared time-resolved spectroscopy. Cerebral blood volume increased to near 10% during head down tilt position compared to the supine position [22]. Our study showed changes in rSO2 over time, with a tendency to increase in both groups. Increased cerebral blood volume resulting from increased PaCO2 and steep head down tilt position might have resulted in a tendency for rSO2 to increase. However, this increase of rSO2 was within 5% in both groups. Similar to our study, changes in rSO2 were within 3% in previous study [22].

Our study includes several limitations. First, transient blood pressure changes above or below of target blood pressure were observed. However, the duration of such blood pressure change was within a minute. We assume that transient blood pressure effect beyond the target blood pressure would not be so potent as to affect the overall results of this study. Second, the operation time of T2 varied depending on surgeon. Although T2 was defined as two hours after pneumoperitoneum and Trendelenburg position, some cases of RALRP had to return to supine position before fulfilling the expected two hours. However, such cases had less than 15 min differences compared to the two-hour fulfilled T2.

In conclusion, both groups showed significant increases in ONSD during CO2 pneumoperitoneum and steep Trendelenburg position compared to baseline. The low blood pressure group demonstrated an effect in maintaining an increase of ONSD less than 10 % during CO2 pneumoperitoneum and Trendelenburg position. However, mean values for ONSD and rSO2 during T0 to T3 did not show any significant differences between the two groups.

ACKNOWLEDGMENTS

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CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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REFERENCES

A retrospective comparison for prediction of optimal length of right subclavian vein catheterization in infants: landmark-based estimation vs. linear regression model

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Background: The optimal insertion length for right subclavian vein catheterization in infants has not been determined. This study retrospectively compared landmark-based and linear regression model-based estimation of optimal insertion length for right subclavian vein catheterization in pediatric patients of corrected age < 1 year.

Methods: Fifty catheterizations of the right subclavian vein were analyzed. The landmark related distances were: from the needle insertion point (I) to the tip of the sternal head of the right clavicle (A) and from A to the midpoint (B) of the perpendicular line drawn from the sternal head of the right clavicle to the line connecting the nipples. The optimal length of insertion was retrospectively determined by reviewing post-procedural chest radiographs. Estimates using a landmark-based equation (IA + AB – intercept) and a linear regression model were compared with the optimal length of insertion.

Results: A landmark-based equation was determined as IA + AB – 5. The mean difference between the landmark-based estimate and the optimal insertion length was 1.0 mm (95% limits of agreement –18.2 to 20.3 mm). The mean difference between the linear regression model (26.681 – 4.014 × weight + 0.576 × IA + 0.537 × AB – 0.482 × postmenstrual age) and the optimal insertion length was 0 mm (95% limits of agreement –16.7 to 16.7 mm). The difference between the estimates using these two methods was not significant.

Conclusions: A simple landmark-based equation may be useful for estimating optimal insertion length in pediatric patients of corrected age < 1 year undergoing right subclavian vein catheterization.

Keywords: Anatomic landmarks; Central venous catheterization; Infant; Pediatrics; Subclavian vein.
INTRODUCTION

Although there are several essential indications for central vein catheterization in small pediatric patients [1], catheterization is not easily achieved in these patients because of their small size and because the vessels can easily collapse. The subclavian vein, which runs underneath the clavicle and lies deeper than the internal jugular vein, is less collapsible and associated with a lower infection rate [2]. Subclavian vein catheterization can be performed safely and efficiently under real-time ultrasound guidance [3].

Central venous catheterization has been successfully performed in pediatric patients using a classical infraclavicular approach with ultrasound scanning at the supraclavicular level [4,5]. However, the optimal length of catheter insertion in pediatric patients undergoing subclavian venous catheterization has not been determined. Most methods suggested to date utilize an approach through the internal jugular vein or are less intuitive [6–9].

A simple landmark-based equation has been suggested for internal jugular vein catheterization [8]. This method allows a catheter tip to be positioned at the optimal target on chest radiographs [8,10]. This method does not require pre-procedural assessment of demographic or radiologic characteristics and the landmark-based distances can be easily measured during the procedure. However, this method has not yet been validated for subclavian catheterization. This study therefore retrospectively assessed the feasibility of the simple landmark-based equation in pediatric patients of corrected age < 1 year.

MATERIALS AND METHODS

Study design and population

The protocol of this retrospective study was approved by the Institutional Review Board of Chungnam National University Hospital (CNUH 2020-04-12), which waived the requirement for informed consent because of the retrospective nature of the study. The medical records and post-procedural notes recorded by the physician who performed the central catheterization via the right subclavian vein between 2016 and 2019 were reviewed. Patients were excluded if they were of corrected age > 1 year. Corrected age was calculated by subtracting the number of weeks born before 40 weeks of gestation from the chronological age [11]. Postmenstrual age was calculated by adding the gestational age and chronological age; thus, a 1-year-old infant born at full-term (gestational age 40 weeks) would have a postmenstrual age of 92 weeks.

Infraclavicular approach to the subclavian vein

All procedures were performed as described previously [5,8]. A linear ultrasound probe was placed at the supraclavicular level with the clavicle at the center of the view. The probe was then directed slightly inferolateral to the superomedial direction. Using an ultrasound-guided in-plane technique, the subclavian vein was punctured with an introducer needle via the infraclavicular route (Fig. 1B). A guidewire was inserted through the needle and the internal jugular vein was scanned to rule out cephalad insertion. The distances between the landmark points were measured during the procedure with a sterile ruler. These measurements included the distances from the needle insertion point (I) to the tip of the sternal head of the right clavicle (A) and from point A to the midpoint (B) of the perpendicular line drawn from the sternal head of the right clavicle to the line connecting the nipples (Fig. 1A). The initial insertion length was determined by adding the distances from I to A and from A to B and fixed after adjusting the length within a 1 cm range by considering the occurrence of an arrhythmia, resistance during aspiration, and the placement of an attachment clip.

Data acquisition

Landmark-based estimation has been used for catheterization in our center since 2016, and the measurements were included in post-procedural notes. Gestational age (weeks), chronological age (weeks), postmenstrual age (weeks), sex, birth weight, height, weight, length of the inserted catheter, and landmark related measurements (I to A [IA] and A to B [AB]) were recorded.

Anteroposterior chest radiographs were obtained after the procedure and reviewed by one author. The vertical distance from the carina to the CVC tip was measured using the Picture Archiving and Communicating System (PACS) (Maroview, Marosis, Korea). The optimal insertion length, defined as the distance at which the catheter tip was positioned at the level of the carina, was calculated as the actual inserted length ± the vertical distance between the catheter tip and the carina (Fig. 2). Correction for vertical distance was based on the consideration that the catheter usually runs vertically from the superior vena cava to the right atrium.
Derivation of the estimation method

Landmark-based estimations (IA + AB) were compared with determined optimal insertion lengths (actual inserted length ± vertical distance). These estimates were subsequently adjusted by determining the optimal intercept that minimizes the mean difference between the determined and estimated optimal insertion lengths.

To determine whether a more precise estimate can be derived from the data of the present study, a regression model was derived by a multiple linear regression analysis that included patient characteristics such as sex, height, weight, birth weight, chronological age, gestational age, postmenstrual age, IA, and AB. Variables with P values < 0.1 on univariate analysis were included in a multivariate analysis. When multicollinearity was detected (based on a variance inflation factor > 10), the more clinically meaningful or practical variable was selected. Finally, a model with the lowest Mallow’s $C_p$ was chosen using a best subset selection approach.

Statistical analysis

The sample size was based on the available data from January 2016 to December 2019. No statistical power calculation was performed before the study. Statistical analysis was performed using R software version 4.0.3 (R Project for Statistical Computing, Austria). Continuous variables are presented as mean ± standard deviation (SD), with 95% confidence interval (CI), or medians and interquartile ranges (IQR) after testing for normal distribution using the Shapiro–Wilk test. The determined and estimated optimal insertion lengths were compared using the Bland-Altman method, which describes agreement between two quantitative measurements [12].
The mean difference (estimated – determined optimal length of insertion) and the 95% limits of agreement (± 1.96 SD of the difference) were calculated. A clinically acceptable limit was not defined a priori. The estimates from the landmark-based equation and the linear regression model were compared using paired t-tests. Two-tailed P values < 0.05 were considered statistically significant.

RESULTS

Of the 51 right subclavian catheterizations performed in 42 pediatric patients, one catheterization was excluded because of patient age. Thus, this analysis included 50 catheterizations in 41 patients (Fig. 3); their demographic and clinical characteristics are summarized in Table 1.

The difference between the optimal insertion length and the initial landmark-based estimation (IA + AB) was 6.04 ± 9.81 mm. For practical reasons, 5 mm was subtracted from each estimate (R² = 0.361). The comparison between the determined optimal insertion length and the adjusted result (IA + AB – 5) is shown in Fig. 4. The mean difference was 1.04 mm, with the 95% limits of agreement being -18.18 mm and 20.26 mm.

Results of univariate and multivariate analyses are presented in Table 2. In the final model, postmenstrual age (weeks), weight (kg), IA (mm), and AB (mm) were selected, with predicted length calculated as 26.681 – 4.014 × weight + 0.576 × IA + 0.537 × AB – 0.482 × postmenstrual age (P < 0.001, adjusted R² = 0.396). A comparison between the determined optimal insertion length and the estimates using the final model is shown in Fig. 5. The mean difference was 0 mm and the 95% limits of agreement were -16.66 mm and 16.66 mm.

The difference between the estimates using the landmark-based equation and the linear regression model was not significant (mean difference –1.04 mm, 95% CI –2.43 to 0.35 mm).

DISCUSSION

This study compared the ability of two models, a landmark-based model and a linear regression model, to predict optimal insertion length during right subclavian vein catheterization in pediatric patients of corrected age < 1 year. Based on Bland-Altman analysis, the linear regression model was slightly more accurate than the simple landmark-based method. For practical reasons, however, we suggest that a simple landmark-based method be used rather than an estimation based on complicated calculations. The results of the present study indicate that, with a slight adjustment, clinicians can estimate the optimal insertion length by simple measurement and arithmetic. This simplicity may enhance the applicability of the method.

Several other methods have been suggested to determine the optimal insertion length of central catheters [7,13–15]. Most of these methods, however, are based on demographic data, may not be intuitive, and/or require complicated intraoperative calculations. Additionally, these methods may not include considerations of inevitable variations due to actual puncture sites. Based on the results of our multivariate analysis, the actual puncture site (IA) was the most important variable for estimating optimal insertion length. In this context, we considered the method suggested by Na et al. [8] (a

Table 1. Demographic and Clinical Characteristics of the Study Subjects and Catheterizations

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total catheterizations (n)</td>
<td>50</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>37.0 (32.0, 38.0)</td>
</tr>
<tr>
<td>Chronological age (wk)</td>
<td>13.5 (4.0, 25.0)</td>
</tr>
<tr>
<td>Postmenstrual age (wk)</td>
<td>47.0 (41.0, 56.0)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2,550.0 (1,870.0, 3,100.0)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>4.1 (3.0, 5.3)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>53.5 (48.5, 59.6)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>25/25</td>
</tr>
<tr>
<td>IA (mm)</td>
<td>40.0 (30.0, 40.0)</td>
</tr>
<tr>
<td>AB (mm)</td>
<td>25.0 (20.0, 30.0)</td>
</tr>
<tr>
<td>IA + AB (mm)</td>
<td>59.9 ± 10.5</td>
</tr>
<tr>
<td>Vertical distance* (mm)</td>
<td>11.3 ± 12.5</td>
</tr>
<tr>
<td>Optimal length† (determined, mm)</td>
<td>53.9 ± 11.4</td>
</tr>
</tbody>
</table>

All catheterizations were considered independent events. Values are expressed as number only, median (1Q, 3Q), or mean ± SD. IA: distance from the insertion point (I) to the tip of the sternal head of the right clavicle (A), AB: distance from point A to the midpoint (B) of the perpendicular line drawn from the sternal head of the right clavicle to the line connecting the nipples. *Vertical distance between the catheter tip and the carina. †Actual inserted length ± vertical distance.

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method that includes the insertion point as an aspect of estimation) practical and also applicable to subclavian vein catheterization. To prevent inconsistencies between predetermined and actual puncture sites, measurements based on landmark points were performed using a sterile ruler immediately after the guidewire was introduced into the vascular lumen.

The infraclavicular approach to the subclavian vein has

**Fig. 4.** Bland-Altman plot of determined and estimated optimal insertion lengths (IA + AB – 5). IA: distance from the insertion point (I) to the tip of the sternal head of the right clavicle (A), AB: distance from point A to the midpoint (B) of the perpendicular line drawn from the sternal head of the right clavicle to the line connecting the nipples.

**Table 2.** Univariate and Multivariate Analysis of Factors Associated with Optimal Insertion Depth in Right Subclavian Vein Catheterization

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
<th>Importance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>95% CI</td>
<td>P value</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>0.506</td>
<td>-0.197 to 1.208</td>
<td>0.154</td>
</tr>
<tr>
<td>Chronological age (wk)*</td>
<td>0.269</td>
<td>0.027 to 0.511</td>
<td>0.030</td>
</tr>
<tr>
<td>Postmenstrual age (wk)*</td>
<td>0.370</td>
<td>0.125 to 0.616</td>
<td>0.004</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>0.004</td>
<td>0.001 to 0.007</td>
<td>0.022</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>2.928</td>
<td>1.459 to 4.398</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>0.663</td>
<td>0.346 to 0.980</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sex, male</td>
<td>2.044</td>
<td>-4.848 to 8.572</td>
<td>0.532</td>
</tr>
<tr>
<td>IA (mm)</td>
<td>0.733</td>
<td>0.388 to 1.078</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AB (mm)</td>
<td>0.752</td>
<td>0.193 to 1.311</td>
<td>0.009</td>
</tr>
</tbody>
</table>

IA: distance from the insertion point (I) to the tip of the sternal head of the right clavicle (A), AB: distance from point A to the midpoint (B) of the perpendicular line drawn from the sternal head of the right clavicle to the line connecting the nipples, CI: confidence interval, NA: not available. *Postmenstrual age was selected instead of chronological age for the multivariate analysis because of their multicollinearity.
several advantages over internal jugular vein catheterization in infants [4]. During cannulation, the internal jugular vein tends to collapse easily in response to pressure from the probe or needle. Moreover, multiple attempts to perform internal jugular vein cannulation can result in hematoma around the blood vessels. In contrast, the subclavian vein is less prone to collapse during cannulation because it is suspended within the soft tissue underlying the clavicle [16]. Also, the infraclavicular approach allows direct visualization of needle advancement, reducing the risk of complications and improving the rate of successful placement. An ordinary linear probe, instead of a hockey-stick shaped probe, was shown to be successful in the infraclavicular approach for infants [5]. However, a skilled in-plane technique is required to prevent serious complications in these small infants.

The optimal position of the central catheter tip remains unclear [17]. Vessel injury and thrombosis may be avoided and proper functioning of the catheter maintained by positioning the catheter tip in the right atrium [18]. However, various problems are associated with deep catheter insertion, including arrhythmia, endocardial injury, and even cardiac perforation and tamponade [19–21]. Critically ill pediatric patients who require central catheterization are especially fragile, making prediction of the optimal insertion length imperative, even for guidewire insertion [22,23]. The wire should not be too deep, which may cause endocardial injury or arrhythmia, or too shallow, which may result in sub-optimal insertion of the catheter into the superior vena cava. Special caution is needed when inserting a straight-tip rather than a j-tip wire [24].

Whether deep or not, the actual intended length of catheter insertion should be based on accurate prediction. The suggested target point of the catheter tip in this study, the carina, can be considered a safe target. The average distance between the carina and the junction of the superior vena cava and right atrium in infants and children undergoing heart surgery has been reported to be 1.5 cm (95% CI 1.3–1.8 cm) [10], with this range (1.3 to 1.8 cm) constituting the clinically acceptable positive limit of error (i.e., estimate – determined value > 0). Based on this consideration accurate than

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**Fig. 5.** Bland-Altman plot of determined and estimated optimal insertion lengths (linear regression model).
the landmark-based method. Nevertheless, however, we concluded that the landmark-based method is also feasible in clinical practice, as the mean difference between the two estimates was –1.038 (95% CI –2.4 to 0.4 mm), making them clinically identical. Also, the estimation based on the regression model requires complicated calculations, which are difficult to be performed intraoperatively. In contrast, the landmark-based method can simply estimate optimal insertion length using intraoperatively measured variables.

This study had several limitations. First, the data used in this study were not purposefully collected. Therefore, information regarding detailed complications and accompanying congenital anomalies was not recorded. Second, several patients required repeated catheterizations. Despite the time gap between procedures, autocorrelation cannot be ruled out. Third, this was a single-center study, with all procedures performed by a single clinician. Our suggested method requires external validation. Fourth, based on the limits of agreement between the estimates and the determined optimal lengths of insertion, the estimation should be regarded as a guide rather than an absolute target.

In conclusion, this study suggests that a simple landmark-based method (IA + AB – 5) can estimate the optimal insertion length of the right subclavian vein catheterization in pediatric patients of corrected age < 1 year.

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CONFLICTS OF INTEREST

Chaeseong Lim has been an editor of the Anesthesia and Pain Medicine since 2020; 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.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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REFERENCES

Pre-operative fasting times for clear liquids at a tertiary children’s hospital: what can be improved?

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Background: The goal of preoperative fasting is to prevent pulmonary aspiration during general anesthesia. Fasting times are often prolonged leading to patient discomfort and risk for adverse events. This retrospective quality improvement survey evaluated effective nil-per-os (NPO) times and causes for prolonged NPO times with the aim to suggest improvement strategies by a newly founded fasting task force.

Methods: Data from all electronic anesthesia records from 2019 at our institution were reviewed for fasting times. Our NPO instructions follow American Society of Anesthesiology guidelines and are calculated based on the patient’s arrival time (90 min before operating room [OR] time). Primary outcome was the effective NPO time for clear liquids, secondary outcomes were incidence of delays and the parental compliance with the NPO instructions. Data are presented as median (interquartile range).

Results: In total 9,625 cases were included in the analysis. NPO time was documented in 72.1% with a median effective NPO time of 7:13 h (7:36). OR in room times were documented in 72.8%, 2,075 (29.5%; median time 0:10 h [0:21]) were earlier and 4,939 (70.5%; median time 0:29 h [0:54]) were later than scheduled. Parental NPO compliance showed a median deviation for clear liquid intake of 0:55 h (8:30).

Conclusions: This study revealed that effective NPO times were longer than current ASA guidelines. Contributing causes include case delays and parental non-compliance to NPO instructions. Thus, task force recommendations include change NPO instruction calculations to scheduled OR time versus arrival time, and encourage parents to give their child clear liquids at the instructed time.

Keywords: Anesthesiology; Fasting; Quality improvement; Surveys and questionnaires.
How to improve fasting times

fasting may lead to hypovolemia and disequilibrium of the metabolic status putting the patient at risk for adverse events including arterial hypotension, difficult intravenous access, or hypoglycemia [6,7]. Isserman et al. [8] and Newton et al. [9] reported in their quality improvement studies methods for optimization in timing of clear liquid fasting. Both studies used the percentage of patients having clear liquids within four hours prior to anesthesia as the improvement criteria. Isserman et al. [8] showed an increase from 20 to 63% and Newton et al. [9] from 19 to 72% after implementing new “nil-per-os” (NPO) instructions allowing more liberal clear liquid fasting for one hour prior to anesthesia. This allowed them to offer eligible children a drink on arrival and reduced their fasting times significantly. This step of reducing the fasting time for clear liquids to one hour was justified by the current evidence showing that one hour of clear liquid fasting is not associated with increased incidence of aspiration [10–14]. Presently, this regimen is corroborated by recently published consensus statements from international anesthesia societies recommending clear liquid intake up to one hour prior to anesthesia [15–18]. However, in the United States, nationwide anesthesia departments follow the current ASA guidelines on clear liquid fasting of two hours prior to anesthesia. Hence, the Isserman et al. [8] and Newton et al. [9] published improvement strategies have not been widely implemented. Thus, other solutions to achieve an optimized clear liquid fasting of two hours with the aim to minimize the negative effects of prolonged fasting need to be described.

The aim of this retrospective quality improvement survey was to evaluate the current effective clear liquid fasting times at our institution, to further investigate causes for prolonged NPO hours and to suggest options to decrease barriers to adherence of current ASA guidelines.

MATERIALS AND METHODS

After approval from the Institutional Review Board at Stanford University School of Medicine (no. IRB-56152) all electronic medical anesthesia records of the year 2019 at the Division of Pediatric Anesthesia of Lucile Packard Children’s Hospital (LPCH, Stanford University School of Medicine, Stanford, CA, USA) were reviewed. Emergent cases were excluded for statistical analysis. All inpatients were also excluded in the statistical analysis due to variability in NPO instructions (NPO from midnight for all liquids and solids to allow more flexibility for scheduling during the next day), which were studied and improved after a quality improvement study published by Nye et al. [19] in 2018.

At our institution patients are instructed to arrive to the hospital at least 90 min prior to their scheduled surgical start time. The NPO instructions are in accordance with the current ASA guidelines and are calculated based on the patient’s arrival time (see Fig. 1).

To investigate and discuss the findings of this retrospective analysis and to further create an improvement plan, a task force was founded. This task force consisted of the chief of the pediatric anesthesia division (JF), a member of the anesthesia quality improvement team (JM), the OR Medical Director (RC), two members of the Pediatric Anesthesia Resource Center team (JM and GD) and an expert on preoperative fasting (ARS).

The primary outcome was to measure the effective NPO time for clear liquid, defined as time from last intake of clear liquids to “in room time”. Secondary outcomes were the incidence of “in room time” compared to scheduled start time and the parental compliance with the NPO instructions (defined as time between instructed and actual NPO time) for patients being allowed to drink clear liquid after 7 AM on their day of surgery.

In addition, all pediatric anesthesia attendings at LPCH were asked to participate in an anonymous online survey to evaluate their willingness to deviate from the existing ASA guidelines for clear liquid fasting. They were asked if they would induce anesthesia (intravenous and mask, respectively) in a child that was fasted for clear liquids for 60, 90, or 105 min.

Data were extracted from our electronic health record (EHR) system, Epic (November 2019 version, Epic Systems, Inc., USA) to Excel (Microsoft Excel, edition 2016, Microsoft Corp., USA) and compiled in SPSS (IBM SPSS statistics, version 23, IBM Co., USA) for statistical analysis. Data are presented as median (interquartile range; minimum–maximum) or count and percent were appropriate. Times are displayed as hh:mm (e.g., 1:46 h = 1 h and 46 min).

A first screening of the data showed very few cases with NPO times under 2 h (n = 88) and some cases with NPO times over 18:00 h (n = 148). This data was validated independently by two authors (ARS and JM). If both reviewers found an error with documentation (e.g., last time for clear fluid intake documented as PM instead of AM), the case was excluded for further analysis. Otherwise, all other cases were included for analysis.
Fig. 1. Displayed is the current nil-per-os (NPO) instruction for our patients based on arrival time. The written text includes the statement the case might be “delayed or cancelled” if the instructions are not followed. NPO for food and candy is always from midnight.
RESULTS

NPO data

A total of 12,623 anesthesia records were extracted from our EHR. From these 540 emergent cases and 2,347 inpatients were excluded prior to analysis. After data validation, 48 cases with NPO times under two hours and 63 cases over 18 h were excluded. Of the remaining 9,625 cases, 6,841 (71.1%) were ambulatory patients and 2,784 (28.9%) were outpatients admitted postoperatively. Patients’ mean age was 8.3 years (10.3; 0.0–68.7) and ASA classifications were as follows: 2,146 (22.3%) ASA-1, 3,929 (40.8%) ASA-2, 3,427 (35.6%) ASA-3, 119 (1.2%) ASA-4 and four missing ASA documentations.

Arrival time to hospital was documented in 9,054 cases (94.1%) and the mean time from arrival to the hospital until effective “in room time” was 1:46 h (1:01; 0:14–15:57 h), with 5.1% of the patients being in the OR less than one hour after arrival and 60.4% being in the OR less than two hours after arrival.

Data for the primary outcome “effective NPO time for clear liquids” were documented in 6,940 cases (72.1%). The median effective NPO was 7:13 h (7:36; 1:36–23:38 h). For 7,067 patients (73.4%) the instructed NPO times were documented with a median of 3:20 h (0:05; 2:00–23:55 h). In 7,014 (72.8%) cases the scheduled “in room time” was documented, 2,075 (29.5%) were in the operating room (OR) earlier than scheduled with a median time earlier of 0:10 h (0:21; 0:01–4:37 h) and 4,939 (70.5%) were in the OR later than scheduled with a median time of 0:29 h (0:54; 0:00–11:06 h).

The number of patients allowed to drink clear liquids after 7 AM until their instructed NPO time was 3,084 patients. The median instructed NPO time for clear liquids was 3:20 h (0:10; 2:00–23:55 h) and the median effective NPO time was 5:14 h (7:39; 1:43–23:38 h). Parental NPO compliance (as defined in the methods section) was calculated and showed a median deviation of clear liquid intake of 0:55 h (8:30; 0:00–18:30 h). A detailed analysis revealed 42% of patients drank clear liquids within 0:30 h prior to the instructed NPO time, 53.7% within 1:00 h prior and 64.3% within 2:00 h prior. Over 30% of the patients allowed to drink clear liquids after 7 AM on the day of surgery had an NPO time for clear liquids longer than 4:00 h.

Online survey

The response rate for the anonymous online survey was 43.9% (25 out of 57 pediatric anesthesia attendings). The majority of anesthesiologists were willing to induce anesthesia via mask (72%) in children who were NPO for clear liquids for at least 105 min and intravenously (84%) if they were NPO for clear liquids for at least 90 min.

Based on the fact that the majority of attendings would be willing to induce anesthesia (both intravenous and mask) 15 min earlier than the recommended ASA 2:00 h (120–105 min = 15 min) and the assumption that in most cases the time from “in room” until anesthesia induction is about 10 min, detailed frequencies of earlier “in room time” were investigated. Of the total of 2,075 (29.5%) cases in the OR earlier than scheduled, 58% are less than 15 min earlier in the OR, 74.7% less than 25 min earlier and 3.5% more than one hour earlier. Based on this data, a change of NPO instructions to “2:00 h prior to the scheduled in room time” may result in a delayed start time in 5.4% of all our annual cases (518 cases per year or two cases per day).

DISCUSSION

This retrospective quality improvement survey investigated the fasting times for clear liquids at a tertiary children’s hospital and the causes for prolonged fasting times. The main findings were that the median effective NPO time for clear liquids is excessively prolonged, only a minority of patients come in the OR earlier than scheduled and a majority of patients do not drink clear liquids up to the time they are allowed.

Similar studies in the past have shown prolonged fasting times for clear liquids with similar results to our study [2–5]. Prolonged fasting of clear liquids has been associated with distress for the patient and the parents [20], a higher incidence of irritability and thirst in the pediatric population [21], increased risk of hypotension during anesthesia induction, and a catabolic state [7]. Therefore, every effort should be undertaken to reduce prolonged fasting times for clear liquids.

The present study helped identify various causes for prolonged fasting for clear liquids. First, the NPO instruction are based on arrival time and thus cause a median lengthening in NPO times for clear liquids by 1:20 h. Parental NPO compliance (as defined in the methods section) was calculated and showed a median deviation of clear liquid intake of 0:55 h (8:30; 0:00–18:30 h).
arrival time. Opponents might argue with the possibility of causing a delay for patients with an earlier than scheduled “in room time”. This argument can be refuted by the following two reasons. First, the incidence of a possible delay for patients going to the OR earlier than scheduled in this study was low (5.4%). Second and more importantly, is the fact that the theoretical delay is based on the hypothesis that all patients have a fasting time of two hours for clear liquids. Based on the data of this study this will rarely be the case. Even Isserman et al. [8] and Newton et al. [9] still reported mean fasting times around six and three hours respectively after implementation of their new NPO instructions of only one hour for clear liquids. Both these quality improvement studies suggested a more progressive regime allowing intake of clear liquids upon hospital arrival [8,9]. Unfortunately, the findings of the present study with 5.1% of patients in the OR less than one hour after arrival and 60.4% in OR less than two hours show that allowing liquid intake upon arrival may result in delays at our institution, since we follow the current ASA guidelines recommending two hours for clear liquid fasting.

NPO compliance for patients instructed to drink after 7 AM must be improved. Only 53.7% patients drank clear liquids within 60 min prior to the instructed NPO time and over 30% of the patients had a NPO time for clear liquids longer than 4 h. This is in accordance with findings from Best et al. [22] showing that patients often choose to fast longer than instructed. One reason for this, at our institution, is the wording of our NPO instructions stating that “If these guidelines are not followed, your child’s procedure or surgery might be delayed or cancelled” (see Fig. 1). The use of punitive statements in NPO instructions should be avoided. Thus, we recommend changing our NPO instructions to encourage or even advocate for the intake of clear liquids at the instructed time. Highlighting the benefits of clear liquid intake (less thirst and anxiety, better behavior and more comfort [20,23–25]) to the parents will support their NPO compliance. This cultural change of encouragement for NPO instructions was previously suggested by other quality improvement studies [8,9]. Fig. 2 shows an example of an encouraging NPO instructions suggested by the task force for implementation at our institution.

Finally, the anonymous online survey revealed that about 50% of the anesthesia attendings would not perform a mask induction on patients who fasted “only” one hour for clear liquids. This practice is in compliance with the current ASA guidelines recommending an NPO time of two hours for clear liquids. Recently published studies showed that one hour of clear liquid fasting is safe [10–14] and have led to publication of several consensus statements by international anesthesia societies recommending clear liquid intake up to one hour prior to anesthesia [15–18]. This dichotomy requires an institutional investigation regarding providers’ biases with regard to more liberal liquid fasting. We suggest initiating an anonymous survey to achieve a departmental consensus agreement and to publish a standard operating procedure. This will allow guidance for all anesthesiology providers.

This study has several limitations that need to be addressed. This is a retrospective study from a single center. Other centers might have different NPO instructions and resulting NPO times. Also, at our institution, consecutive cases do not have concurrent anesthesia times. Other institutions may have the ability to induce the next patient in a separate induction room and therefore may need to add additional NPO buffer time to prevent delays. Some of these patients with excessive NPO times may have been placed on intravenous maintenance fluids and therefore, should have been excluded from analysis. The causes for a delayed start (pa-
tient not ready, anesthesia or surgical delays) were not investigated in detail and also case cancellations for NPO violations were not investigated. Finally, a possible improvement of clear liquid fasting times with the changes could not be reported as these changes are recent. Both Isserman et al. [8] and Newton et al. [9] reported a period of over 2 years until improvement was seen. Hence, we thought it important to present the results of our study as it could have implications for other institutions.

Based on the findings of this retrospective quality improvement survey the task force highly recommends the following change in practice at LPCH:

1. Allowing patients to drink clear liquids calculated on the scheduled “in room time”.
2. Parents should be advised to give their child something to drink at the instructed time even if they have to wake up their child.
3. Based on the evidence that one-hour clear liquid fasting is safe, attempt to minimize delay anesthesia induction in cases when the NPO time for clear liquid fasting is “only” 105 min.

How to implement in daily clinical routine:

1. Use readily available anesthesia diet orders in the electronic medical record for placing the NPO orders. This will increase adherence and cause less calculation mistakes.
2. With regards to the NPO instructions, we use clear verbiage on our internet website, as well as on the paperwork handed out to families during the pre-anesthesia visit. It is of great importance to go through these instructions in detail with the family and actively encourage them to give fluids up to the allowed time.
3. For patients unable to tolerate prolonged NPO times (e.g., neonates), these cases should be scheduled as first case in the morning to minimize the risk of delayed case start.
4. Investigation of cases with a high incidence of taking longer than scheduled. This will allow more accurate scheduling for the future and decrease the risk of delays for the cases to follow.

In conclusion, we identified three factors that cause prolonged fasting times at our institution. Since prolonged fasting can be associated with hypovolemia and disequilibrium of the metabolic status and thus, puts patients at risk for adverse events including arterial hypotension, difficult intravenous access, or hypoglycemia every effort should be attempted to minimize prolonged fasting times. Our results have led us to the conclusion that our NPO times should be based on the scheduled “in room time”, that we should use encouraging instead of punitive language for NPO instructions and that anesthesia staff should not delay anesthesia induction if the fasting time for clear fluids is close to 2 h. Each institution should review their performance on fasting times and identify areas of improvement.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are not publicly available due (Stanford University Patient Privacy Policy) but are available from the corresponding author on reasonable request.

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tion: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Task Force on preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration. Anesthesiology 2017; 126: 376-93.


Central venous catheterization is frequently performed during general anesthesia, mainly for fluid administration and monitoring of central venous pressure. In addition, the need for frequent blood sampling can also be a reason for central venous catheterization to reduce the pain or fear of needle insertion. Since pediatric patients with moyamoya disease (MMD) are at risk of ischemic attack when crying or undergoing physical or emotional stress, a central venous catheter would be helpful for postoperative blood sampling or fluid management to prevent these events.

A peripherally inserted central catheter (PICC) is a good option for central venous access [1] with good compliance, low complication rate [2,3], and readiness for ambulation after surgery, compared to the internal jugular or subclavian veins. However, it is rarely selected by anesthesiologists in the operating room. While PICC can be inserted at the bed-
side or under fluoroscopic guidance prior to surgery for adults, PICC insertion for pediatric patients is not easy, and they require sedation for the procedure in most cases. Under general anesthesia, ultrasound is readily applicable to pediatric patients without causing radiation hazards compared to fluoroscopy, which is frequently used as a guide for PICC insertion.

We recently introduced a policy to insert the PICC under ultrasound guidance after induction of general anesthesia in pediatric patients undergoing surgery for MMD. We report our cases along with a summary of the success and complication rates.

**CASE REPORT**

**Ethics statement**

This report was approved by the Institutional Review Board of Seoul National University Hospital (no. 2004-231-1119), and the requirement for obtaining informed consent was waived. The reason for the exemption from consent was as follows: First, obtaining informed consent from the patients was not feasible because they had already been discharged from the hospital at the moment we started to review the cases. Second, there was no reason to assume disagreement regarding the use of data from the patients, and there was no chance of affecting any of the patients’ treatment or prognosis.

**Study population**

We reviewed 30 cases of ultrasound-guided PICC insertion after anesthetic induction in pediatric patients undergoing surgery for MMD between January 2020 and April 2020. The baseline characteristics are shown in Table 1. Seventeen (56.7%) patients had previously undergone neurosurgery with central venous catheterization using one of the internal jugular veins. Patients with connective tissue disease or vascular disease other than MMD, any skin lesion in the upper extremity, and unstable vital signs on anesthetic induction were excluded from the PICC insertion.

**Catheter insertion technique**

After conventional induction of general anesthesia, the patient was positioned for PICC insertion in the supine position, and the right upper arm was abducted [4]. After positioning, the basilic or cephalic vein was evaluated using an ultrasound device (E-CUBE i7, Alpinion Medical Systems Co., Ltd., Korea or Sonosite X-Porte, Fujifilm Sonosite, Inc., USA) to select the venipuncture site. If the basilic vein was selected, the elbow was flexed at 90°, while it was extended to the cephalic vein. The patient’s right arm was covered with a surgical drape after sterilization. Turbo-Ject® power-injectable PICC (Cook Medical LLC, USA) with a size of 3 or 4 Fr was prepared. Even though 4-Fr catheters are recommended for veins larger than 4 mm in diameter [5], a larger catheter size may be related to a higher risk of thrombosis [6]. In most cases, we used 3-Fr catheters in an effort to use a catheter as small as possible to prevent thrombosis. Catheters sized 4 Fr were used only for patients weighing > 70 kg. Before venipuncture, the length of catheter insertion was determined by measuring the distance between the targeted venipuncture site and the sternal notch [7]. The catheter was then trimmed according to the required length. The targeted vein was punctured under ultrasound guidance, followed by the insertion of a 20-gauge intravenous BD angiocath™ (Becton, Dickinson, and company Korea, Korea) catheter. To ensure stability, we tried to maintain a distance of at least 4 cm between the antecubital fossa and venipuncture site [8]. Subsequently, a guidewire was inserted via an intravenous catheter. An introducer was inserted along the guidewire after a minimal skin incision was made at the venipuncture site. After removal of the guidewire, the PICC was inserted through the introducer and advanced until the entire catheter was inserted. During the advancement of the catheter,

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>20/10</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>7.5 (6, 9)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>124.0 (115.7, 146.2)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>28.4 (21.7, 46.6)</td>
</tr>
<tr>
<td>Selected vein</td>
<td></td>
</tr>
<tr>
<td>Basilic</td>
<td>21 (70.0)</td>
</tr>
<tr>
<td>Cephalic</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>Failure for both</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>Vein diameter (mm)</td>
<td>4.0 ± 0.9</td>
</tr>
<tr>
<td>Vein depth (mm)</td>
<td>5.4 (4.1, 8.5)</td>
</tr>
<tr>
<td>Catheter size (Fr)</td>
<td>3 (86.7)</td>
</tr>
<tr>
<td></td>
<td>4 (13.3)</td>
</tr>
</tbody>
</table>

Values are represented as number (%), median (1Q, 3Q), or mean ± SD.
the patient’s head was turned to the ipsilateral side. The arm was then moved cephalad in an effort to facilitate successful insertion [9]. The function of the PICC was tested by aspiration of blood and flushing with normal saline through the catheter.

### Confirmation of the catheter tip

Immediately after insertion of the catheter, the right internal jugular vein was traced using ultrasound to confirm that the catheter did not enter the right internal jugular vein. When the catheter was observed in the right internal jugular vein, the catheter was withdrawn slightly and then reinserted until the catheter was completely inserted but not visible in the right internal jugular vein. If possible, the right subclavian vein was also visualized to ensure that the catheter had not migrated into the right innominate vein.

After the end of the surgery, the position of the tip of the catheter was checked via chest radiography (CXR) at the intensive care unit or the post-anesthesia care unit. The tip position was classified into three categories: “Optimal” for those located within a 3-cm margin from the cavo-atrial junction, “suboptimal” if they were within the superior vena cava (SVC) or the right atrium, but located outside the 3-cm margin from the cavo-atrial junction, or “malpositioned” in cases involving vessels at locations other than the SVC [10]. We defined success as the optimal or suboptimal position of the catheter tip in the postoperative CXR.

### Statistical analysis

Demographic data, history of previous surgery, vein selected for puncture, depth from skin and diameter of the selected vein, determined insertion length of the catheter, the success rate at the first attempt, overall success rate, number of insertion attempts, reasons for failed attempts, postoperative repositioning of the catheter, duration of postoperative catheter indwelling, and functioning of the catheter were reviewed. Immediate and long-term complications, including hematoma formation, thrombosis, infection, insertion site oozing, skin reactions, and catheter migration, were also reviewed. The Pearson correlation coefficient between the patient height and the determined insertion length of the catheter was calculated. Statistical analyses were performed using SPSS® statistics version 23.0 (IBM, USA).

### Outcomes of PICC insertion

Among the 30 patients, the procedure was completed in 27 (90.0%) patients, while we failed to introduce the catheter in the other 3 patients. Twenty-two (73.3%) cases showed successful PICC with optimal or suboptimal positioning of the catheter tip on confirmation with CXR. Insertion was successful in the first attempt in 19 patients. Detailed information on the insertion attempts is presented in Table 2.

Upon confirmation with postoperative CXRs for the completed cases, 5 (16.7%) cases showed malpositioning of the catheter, 3 in the right internal jugular vein, and 2 in the left brachiocephalic vein. Fig. 1 shows examples of CXRs for the successful placement and malpositioning of the catheter tip. Among the malpositioned cases, the basilic vein was selected in four cases and the cephalic vein was selected in one case. In one case of malpositioning of the internal jugular vein, the PICC was revised in the angiography room the day after. In another case of malpositioning of the internal jugular vein, the catheter was withdrawn by 4 cm. In the remaining 3 malpositioned cases, the catheter was used without repositioning. In 6 cases, the catheter tip was located deeper than expected. In these cases, the catheter was withdrawn by a median (1Q, 3Q) of 3.8 (3.1, 5.5) cm. Two of the withdrawn cases involved follow-up CXRs, which confirmed the withdrawal of the catheter to the proximal end of the right internal jugular vein.

### Table 2. Results of Peripherally Inserted Central Catheter Insertion

<table>
<thead>
<tr>
<th>Subject</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheter insertion length (cm)</td>
<td>28 (26, 32)</td>
</tr>
<tr>
<td>Number of attempts to success</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>19 (63.3)</td>
</tr>
<tr>
<td>2</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>3</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>Reason for failed attempts (n = 17)</td>
<td></td>
</tr>
<tr>
<td>Venipuncture failure</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>Guidewire insertion failure</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Dilation failure</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>Catheter advancement failure</td>
<td>9 (52.9)</td>
</tr>
<tr>
<td>Catheter tip position</td>
<td></td>
</tr>
<tr>
<td>Optimal*</td>
<td>14 (46.7)</td>
</tr>
<tr>
<td>Suboptimal†</td>
<td>8 (26.7)</td>
</tr>
<tr>
<td>Malpositioning‡</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td>Failure§</td>
<td>3 (10.0)</td>
</tr>
</tbody>
</table>

Values are represented as median (1Q, 3Q) or number (%). *Located within a 3-cm margin from the cavoatrial junction. †Located within the superior vena cava (SVC) or the right atrium and could be easily repositioned by the withdrawal of the catheter. ‡Locations other than the SVC. §Failed to insert the catheter.
subclavian vein. In one case, the insertion length was shorter than expected to an extent of 5 cm, and there was no adjustment.

In 3 patients, the catheter was unexpectedly withdrawn during transportation of the patient from the operating room to the intensive care unit, while re-insertion of the catheter was not performed. All successful cases showed intact catheter function, with no reported immediate complications such as hematoma, thrombosis, skin irritation, or bleeding. The median (1Q, 3Q) duration of indwelling was 7 (6, 8) days, and the total indwelling time for all subjects was 184 PICC-days with no reported complications or complaints of discomfort. There was a strong positive correlation between the patient’s height and the insertion length of the catheter, with a Pearson correlation coefficient of 0.906 (P < 0.001).

Four patients were included twice in our data, and all showed successful insertion during the first operation. In the second operation, the four cases showed a failure of PICC insertion, malpositioning to the contralateral side, successful insertion in the same vein, and successful insertion in the alternate vein (cephalic–basilic).

We did not survey patient satisfaction with PICC after surgery. However, neurosurgeons in charge of their in-hospital care reported an overall increase in patients’ comfort and stability during the hospital stay with PICC compared to access via the internal jugular or subclavian veins.

**DISCUSSION**

We summarized cases of PICC insertion under ultrasound guidance after induction of general anesthesia in pediatric patients undergoing surgery for MMD with successful positioning of the catheter tip in 22 out of 30 cases.

In recent studies, success rates defined as proper positioning of the PICC catheter with ultrasound-guided insertion have been reported to be about 81.2% and 94.4% [10,11] in adults and 83.9% [12] in children. Our success rate of 73.3% was relatively lower than these results. In our cases, catheter insertion was performed during anesthesia and prior to surgery. As we just introduced the policy of PICC insertion in our department, the proficiency of the practitioner might be a cause for the lower success rate. Moreover, since we reviewed only a small number of cases, the success rate may be inconsistent with previous data. Among the three cases of failed insertion, it was difficult to advance the catheter into the right subclavian vein with or without the obturator in two cases, and advancement of the introducer was impossible in the other case. Reports of common reasons for PICC insertion failure are difficult to find in the literature, so we could not compare our results with those of previous studies.

The incidence of malpositioning of the catheter tip is reported to be higher with ultrasound guidance than with fluoroscopic guidance [13] and varies from 8.4% to 27% [10,13]. In our study, the malpositioning rate of the inserted cases was 18.5%, which is consistent with these results. Although we checked via ultrasound immediately after catheter placement, upper limb PICC in children may move with arm movement to an extent of 2.2 rib spaces [14], which can be an explanation for this malpositioning. Abduction of the right upper arm during the procedure might have affected the migration of the

![Fig. 1. Examples of postoperative chest radiographs for confirmation of the tip of peripherally inserted central catheters. The tip is located at the superior vena cava (A), ipsilateral internal jugular vein (B), and contralateral brachiocephalic vein (C).](image-url)
catheter tip since the arm was abducted during the surgery and immediate postoperative period. We might have had a better agreement between CXR and ultrasound if CXR was checked immediately after insertion. However, since we wanted to avoid exposing patients to additional radiation, we decided not to check CXR immediately, but to rely on ultrasound and routine postoperative CXR. This was possible because our primary reason for PICC insertion was acquiring a stable route of blood sampling and fluid administration, but not monitoring the central venous pressure.

Immediate complications associated with PICC insertion are reported to be rare, with a global complication rate of 30.2% during indwelling and 11.1 per 1000 PICC-days [15]. In our study group, there were no records of any complications associated with PICC. In contrast, in our previous study, patients maintained the PICC for a median of 17 days, ranging from 2 to 174 days [15], and the meantime to the onset of complications was 16.1 days. The relatively short catheter maintenance period may have affected our complication-free outcomes. In three cases, however, accidental withdrawal of the catheter occurred during transportation of the patient, which indicated the need for more caution.

Although some reports have described landmark-based determination of PICC insertion length, they are limited to adults [7]. Since there is no standardized method to determine the appropriate length of PICC insertion in children and no fluoroscopy was available, we simply measured the distance between the targeted insertion site and the sternal notch [7]. The insertion length was optimal in approximately half of the cases and was acceptable (optimal and suboptimal combined) in 81.5% of the inserted cases. Although there is one report on the landmark-based determination of the length of PICC in children with preliminarily taken CXRs [16], we did not employ this technique because of the absence of images that cover the right arm and the chest altogether in our institute.

While PICC insertion helps patients in postoperative management in many ways, it does not change or help in anesthetic management during surgery. From the anesthesiologists’ perspective, the advantage of PICC is the relatively high safety compared to other central venous catheterization methods.

Our study had some limitations. First, as we only included elective surgeries for MMD and patients were relatively healthy except for that, our cases had a relatively short indwelling duration of PICC and a low complication rate. These may be valuable data, but the findings are not generalizable to patients with worse general conditions or those requiring extended indwelling. Further studies including other populations are needed to obtain more generalized data. Second, as patient satisfaction was not adequately recorded and compared to that for conventional central venous catheterization, we cannot claim that PICC is more patient-friendly than conventional insertions. However, since the median duration of indwelling was approximately 7 days, it is credible that the insertion site of the forearm will be much more comfortable to maintain than the neck or chest. A prospective study comparing PICC and other methods of central venous access will provide an answer to this concern. Third, the elapsed time of insertion was not recorded, even though there were some cases with multiple attempts. Further prospective studies are required to include the time measurements.

In conclusion, PICC can be successfully introduced to pediatric patients undergoing surgery for MMD during anesthetic management without serious complications. Further prospective studies including insertion depth determination, insertion technique, and comparison with other forms of central venous access will be needed to improve our clinical practice for pediatric patients who require central venous access.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

REFERENCES


Liver transplantation of a patient with extreme thrombocytopenia - A case report -

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Background: Patients with chronic liver disease (CLD) planned for liver transplantation (LT) often show severe thrombocytopenia, but there is a lack of evidence in deciding the threshold for prophylactic platelet transfusion.

Case: A 47-year-old female with acute liver failure was referred for LT. Despite daily transfusion of platelets, platelet counts remained under 10,000/µl. During LT, 2 units of single donor platelets (SDP) were transfused. Although platelet counts remained extremely low (3,000–4,000/µl) no diffuse oozing was observed and the blood loss was 860 ml. Postoperatively, there was no sign of active bleeding or oozing, and the patient received only 1 unit SDP transfusion.

Conclusions: CLD patients may have severe thrombocytopenia. However, primary hemostasis may not be significantly hindered due to the existence of rebalanced hemostasis. Prophylactic platelet transfusion in these patients should not be decided based on platelet counts only, but also take other coagulation tests and clinical signs into consideration.

Keywords: Liver transplantation; Platelet transfusion; Rebalanced hemostasis; Thrombocytopenia.

CASE REPORT

A 47-year-old female (body weight 49.6 kg, height 159 cm) suffered from acute liver failure due to alcoholic hepatitis. The patient was a heavy drinker and was hospitalized due to mental changes two months prior to LT. She received steroid treatment for severe alcoholic hepatitis, but it was tapered...
due to lack of response. Treatment for hepatic encephalopathy and endoscopic variceal obturation for gastric variceal bleeding was performed as well. One week before LT, she was intubated due to dyspnea caused by pulmonary edema, probably due to excessive transfusion and fluid treatment after hematemesis.

She was transferred to our hospital six days prior to LT. Initial laboratory results were hemoglobin 8.7 g/dl, hematocrit 26%, platelet count 2,000/µl, prothrombin time (PT) 29.0 s with an international normalized ratio (INR) 2.73, and activated partial thromboplastin time (aPTT) 49.9 s. Computed tomography revealed liver cirrhosis, splenomegaly, and multiple collateral vessels in the abdominopelvic cavity. Esophagastroduodenoscopy revealed large gastric varices and portal hypertensive gastropathy. Echocardiography was normal. The patient had very severe thrombocytopenia; despite daily transfusion of 6 to 18 units of leukocyte-depleted platelet concentrate (LDPC), platelet counts remained under 10,000/µl. However, there was no spontaneous bleeding despite persistent severe thrombocytopenia. In the intensive care unit (ICU), along with transfusion, ventilator care and continuous renal replacement therapy was done until LT.

A deceased donor liver was allocated and the intubated patient was transferred to the operating room. After standard monitoring, general anesthesia was induced with intravenous thiopental sodium 50 mg, atracurium 50 mg, and sevoflurane. The right radial artery, right femoral artery, and right femoral vein were cannulated for monitoring and sampling. A 9-Fr catheter (ARROW MAC, Teleflex, USA) was inserted into the right internal jugular vein and a pulmonary artery catheter was inserted to monitor pulmonary artery pressure, continuous cardiac output, and mixed venous oxygen saturation. Anesthesia was maintained with oxygen, air, isoflurane, and atracurium.

On the day of surgery, only 2 units of single donor platelets (SDPs) were available in the hospital. Therefore, we planned to transfuse the 2 units of SDPs throughout the surgery. Perioperative coagulation profiles and non-activated thromboelastometry (NATEM) results are shown in Table 1. Despite continuous transfusion of platelets, platelet count remained at 3,000–4,000/µl. Although platelet count was very low, no diffuse oozing was observed in the operating field and blood loss expressed as lost red cell mass was 860 ml [4]. Crystalloid 3,050 ml, 5% albumin 550 ml, 4 units of packed red blood cells, 550 ml of autotransfusion, 7 units of fresh frozen plasma, and 2 units of SDPs were infused during the 300-min LT procedure. Continuous infusion of norepinephrine (0.01–0.2 µg/kg/min) was maintained throughout the surgery and the recipient was transferred to the ICU.

Postoperatively, there was no active bleeding or oozing, and the recipient received only 1 unit of SDPs on the day after surgery. Although thrombocytopenia due to peripheral sequestration and destruction by splenomegaly was suspected, laboratory tests and consultation with the department of hemato-oncology were performed to determine the cause of persistent very severe thrombocytopenia. Many spherocytes and schistocytes (2–3/high-power field) were observed in peripheral blood smear. Positive direct antiglobulin test and increased D-dimer suggested immune hemolytic thrombocytopenia. Bone marrow biopsy was recommended to confirm whether thrombocytopenia was peripheral in origin rather than from production failure. Also, con-

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<th>Table 1. Coagulation Profiles and Non-activated Thromboelastometry (NATEM) Results during and after Liver Transplantation</th>
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<td><strong>Time of sampling</strong></td>
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PT (INR): prothrombin time (international normalized ratio) (reference range: 0.80–1.30), aPTT: activated partial thromboplastin time (reference range: 30–40 s), CT: clotting time (reference range: 300–1,000 s), CFT: clot formation time (reference range: 150–700 s), α angle: alpha angle (reference range: 30–70°), MCF: maximum clot firmness (reference range: 40–65 mm), LI 60: lysis index 60 (reference range: 76–96%), POD: postoperative day, NA: not available. *Protamine-treated Fig. 1. Perioperative changes in platelet count.
consultation recommended that if thrombocytopenia persists, splenectomy may be required. However, without further treatment, platelet counts started to increase from postoperative day (POD) 4 and spontaneously recovered to over 100,000/µl on POD 10 (Fig. 1). On POD 20, the patient was discharged without major complications.

**DISCUSSION**

To the best of our knowledge, this case reports the lowest preoperative platelet counts for a patient undergoing LT. There have been reports of patients with very severe thrombocytopenia undergoing extrahepatic mass excision (19,000/µl) [5] or laparoscopic splenectomy (1,000/µl) [6], but LT is usually considered to be more complex with a greater risk of bleeding, and thus a more challenging procedure.

In CLD patients, thrombocytopenia is a very common complication with multifactorial origins. An increase in splenic sequestration due to hypersplenism, a decrease in thrombopoietin production, an increase in platelet destruction due to autoantibodies, and an increase in platelet consumption due to cirrhosis-related hypercoagulability all can play a role [7,8]. Although thrombocytopenia in these patients may be severe, this is to some extent compensated for by an increase in von Willebrand factor (vWF) and a decrease in a disintegrin and metalloprotease with thrombospondin type 1 motif 13 (ADAMTS13) resulting in rebalanced hemostasis, thus reducing the risk of bleeding [7,9,10].

During LT, 2 units of SDPs were transfused slowly starting just after the induction of anesthesia until the end of surgery. Although platelet counts were under 10,000/µl throughout surgery, no diffuse oozing was observed in the operating field. Platelet counts remained under 10,000/µl for 5 days after LT, and there was no evidence of significant postoperative bleeding. This may reflect that in CLD patients with very severe thrombocytopenia, primary hemostasis may not be as impaired as expected. There seems to be little evidence to suggest a threshold for platelet transfusion in these patients [10], and therefore further studies are warranted.

Platelet count reaches its nadir at POD 6, and then starts to increase [11]. This is in line with what we observed in the present case. Platelet count remained steady at 4,000/µl after LT until it started to rise dramatically, reaching 126,000/µl at POD 10. As portal hypertension is resolved after LT, platelet count increases and hypersplenism is reversed [12]. Thromboelastometry results support this. Maximum clot firmness [MCF], which reflects platelet count, improved along with all other indicators at POD 6. Even when platelet counts were very low, lysis index 60 (LI 60) was relatively normal, which might contribute to lowering bleeding tendency by maintaining clot stability. The fibrinolytic system may also be in balance in patients with CLD, due to the concomitant decrease in antifibrinolytics (antiplasmin, thrombin activatable fibrinolysis inhibitor), and plasminogen [10]. Thus, in

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**Fig. 1.** Perioperative platelet counts. SDP: single donor platelets, PC: platelet counts, POD: postoperative day.

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CLD patients, conventional coagulation tests such as PT, aPTT, and platelet count may not fully reflect complex changes in the coagulation system. Although it is difficult to confirm the presence of rebalanced hemostasis, thromboelastography (TEG) or rotational thromboelastometry (ROTEM) may be helpful in assessing coagulopathy in these patients [5]. Also, clinical signs such as bruising, purpura, epistaxis, gingival bleeding, menorrhagia, and bleeding associated with invasive procedures may exist in the absence of rebalanced hemostasis.

Although platelet transfusion is the mainstay of clinical management of severe thrombocytopenia, the platelet count at which transfusions are indicated remains controversial in CLD patients undergoing invasive procedures. Generally, according to transfusion guidelines, platelets are given routinely before interventions in uncomplicated thrombocytopenic patients with a count of less than 10,000–20,000/µl [2,13]. Since patient platelet count in the present case were consistently under 10,000/µl, 6 to 18 units of LDPC were transfused daily before LT, but platelet count remained under 10,000/µl. This correlates with findings that the platelet counts of CLD patients with thrombocytopenia do not typically increase significantly after platelet transfusion [14]. We also transfused 2 units of SDPs during LT and this, along with rebalanced hemostasis, may have had a role in hemo-stasis during surgery. Nevertheless, immune hemolytic thrombocytopenia was not clearly ruled out and prophylactic platelet transfusions may not provide additional benefit in this patient, it would have been worthwhile trying less platelet transfusion in perioperative period. It was difficult to determine the cause of thrombocytopenia in this case. However, considering that the platelet count did not rise even after multiple blood transfusions, and normalized without any specific treatment after LT, it can be assumed that hypersplenism due to portal hypertension was the main cause of thrombocytopenia rather than production failure or other immunologic reactions.

Although the practice of transfusion has become very safe, there still are some risks that clinicians should be aware of, especially in LT patients, including infection, alloimmunization, and febrile and nonhemolytic reactions. Apart from the possibility of developing inflammatory reactions or bacterial/viral infections, platelet transfusion during LT is suspected to increase postoperative mortality due to acute lung injury [15]. Therefore, the potential benefit and risk of harm should be judged by clinicians making decisions regarding platelet transfusion.

In conclusion, even in CLD patients with very severe thrombocytopenia, primary hemostasis may not be significantly hindered. Prophylactic platelet transfusion in these patients should not be decided based only on platelet count, but should also take into account other coagulation tests and clinical signs of bleeding.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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REFERENCES

Tachycardia-polyuria syndrome is characterized by the onset of polyuria after tachycardia with a heart rate (HR) of ≥ 120 beats/min persisting for at least 30 min [1]. Multiple case reports of polyuria in patients with paroxysmal supraventricular tachycardia have been published [1–3]. A reduction of antidiuretic hormone (ADH) and secretion of atrial natriuretic peptide (ANP) are known to be involved in this phenomenon [4,5]. This phenomenon more commonly affects patients with paroxysmal atrial fibrillation (a-fib) than it does those with a valvular disease or chronic heart failure [1,3,6]. Here, we report a case of a-fib during insertion of a swan-ganz catheter, followed by polyuria during living-donor liver transplantation surgery.

Background: Tachycardia-polyuria syndrome is characterized by polyuria occurring because of tachycardia with a heart rate of ≥ 120 beats/min lasting ≥ 30 min. We report such a case occurring after swan-ganz catheterization.

Case: A 41-year-old male was scheduled for living-donor liver transplantation. After general anesthesia, atrial fibrillation occurred during swan-ganz catheterization, and polyuria developed 1 h later. During the anhepatic phase, the patient’s heart rate increased further, and cardioversion was performed. After a normal sinus rhythm was achieved, the patient’s urine output returned to normal.

Conclusions: The patient’s polyuria seemed related to the iatrogenic atrial fibrillation occurring during swan-ganz catheterization. Although we did not measure atrial natriuretic peptide, an increase in its concentration may have been the main mechanism of polyuria, as natriuresis was observed.

Keywords: Antidiuretic hormone; Atrial fibrillation; Atrial natriuretic peptide; Polyuria; Swan-ganz catheter.

CASE REPORT

This case report was exempted from the need of obtaining the patient’s informed consent by the Institutional Review Board (IRB) of Asan Medical Center (no. 2021-0047).

A 41-year-old male, diagnosed with hepatocellular carcinoma, was admitted for a living-donor liver transplant. The patient (179.1 cm and 87.7 kg) was a carrier of the hepatitis B virus and had liver cirrhosis with a Child-Pugh score of 5 and a model for end-stage liver disease score of 7. The patient had no notable medical history other than hypertension. No notable findings were obtained from the chest X-ray, electrocardiogram (ECG), transthoracic echocardiography.
raphy, coronary artery computed tomography, brain magnetic resonance image (MRI), lung function test, blood tests, and arterial blood gas analysis performed at the time of admission.

After arrival at the operating room, the patient’s blood pressure, ECG, and oxygen saturation (SpO₂) were monitored; all his vital signs were normal. Anesthesia was induced with midazolam (5 mg), propofol (130 mg), rocuronium (100 mg), and fentanyl (100 µg). Following endotracheal intubation, anesthesia was maintained with desflurane (4–5%) and continuous infusion of fentanyl and rocuronium. We placed a catheter in the right radial artery, two catheters in the right internal jugular vein, and a catheter in the right subclavian vein to secure access to a central vein.

While inserting a swan-ganz catheter, the patient’s ECG revealed a-fib with a rapid ventricular response (RVR) (Fig. 1). We administered a beta blocker (esmolol), which did not markedly change the ECG. The patient’s vital signs at the time were as follows: arterial blood pressure, 107/71 mmHg; HR, 137 beats/min; SpO₂ 99%. The arrhythmia lasted for about 9 min, and a normal heart rhythm was spontaneously achieved. To avoid further a-fib, we retracted the swan-ganz catheter to a depth of 15 cm and attempted to fully reinsert it after 20 min; however, a-fib with a RVR occurred again (Fig. 2). The patient was immediately given a beta blocker (esmolol), but the arrhythmia persisted; thus, an anti-arrhythmic agent (amiodarone) was continuously infused. The patient’s other vital signs remained stable, and transesophageal echocardiography also revealed no notable findings other than a-fib. Hence, we decided to continue the surgery while carefully

![Fig. 1. This is atrial fibrillation occurred when swan-ganz catheter was inserted. ECG: electrocardiogram, ABP: arterial blood pressure.](image1)

![Fig. 2. This is atrial fibrillation occurred when swan-ganz catheter was re-inserted. ECG: electrocardiogram, ABP: arterial blood pressure.](image2)
monitoring the patient.

Urine output (U/O) measured as soon as the surgery commenced was abnormally high (1,000 ml/h). We suspected polyuria due to tachycardia [2,3,5-7] and, thus, performed urine analysis (U/A) and plasma ADH testing. The results indicated natriuresis (sodium clearance, 18.6 ml/min; osmolar clearance, 16.6 ml/min; 2 × urine sodium/urine osmolarity, 0.88) (Fig. 3). During the anhepatic phase, the patient’s HR increased further and exhibited hemodynamic instability; hence, direct current (DC) cardioversion (50 J) was performed, after which a normal rhythm was achieved (Fig. 4). U/O measured one hour later was markedly decreased and natriuresis was reduced (sodium clearance, 3.7 ml/min; osmolar clearance, 3.6 ml/min; 2 × urine sodium/urine osmolarity, 0.81) (Fig. 3).

The surgery proceeded without notable problems, after which the patient was transferred to the intensive care unit (ICU). The patient’s ECG revealed normal rhythms until the end of surgery. At the ICU, the patient exhibited a normal U/O and ECG, with stable vital signs, and, after being transferred to a general ward, the patient was discharged without any further problems.

**DISCUSSION**

We reported a case of tachycardia-polyuria syndrome that occurred during insertion of a swan-ganz catheter in a liver transplant patient.

According to Wood [1] and Luria et al. [3], tachycardia-polyuria syndrome is defined as polyuria that occurs in approxi-
Approximately half of patients with paroxysmal supraventricular arrhythmias faster than 110 beats/min lasting for ≥ 20 min in the absence of left ventricular failure and stenotic valvular lesions, and there are no clear diagnostic criteria for this syndrome. ADH and ANP are known to be potentially involved in the mechanism underlying tachycardia-polyuria syndrome [2,4,5,7,8]. In addition to receiving blood into the heart and releasing it into the ventricles, the atria also serve the function of detecting and regulating the intravascular volume. This process, which begins with the atrial receptors, is known to involve neuronal and hormonal networks such as ADH and ANP [4]. An elevation of venous return in the body leads to atrial distention, which stimulates the atrial receptors [9]. These receptors depolarize the afferent vagal nerve to decrease the efferent sympathetic and vasomotor tones of the renal nerve, and to reduce ADH activity, thereby inducing diuresis [6].

Polyuria refers to an abnormally high output of diluted urine (i.e., ≥ 3 L/24 h or ≥ 40–50 ml/kg/24 h). It can be caused by a variety of factors, and these conditions are collectively referred to as polyuria-polydipsia syndrome. The causes can be broadly classified into three factors: central diabetes insipidus (CDI), nephrogenic diabetes insipidus (NDI), and primary polydipsia. Because the causes and treatments for each of these factors differ, differential diagnosis is crucial [10]. The patient in this case had no abnormal preoperative brain MRI findings and had no history of endocrine diseases such as diabetes mellitus or renal diseases. Further, the patient had a normal electrolyte balance during surgery, and none of the medications administered intraoperatively were known to induce polyuria. Therefore, we could eliminate CDI and NDI from the diagnosis. The patient developed polyuria during induction of anesthesia, allowing us to eliminate volume overload. In essence, the patient’s polyuria seemed related to the iatrogenic a-fib that occurred during insertion of the swan-ganz catheter during induction of anesthesia.

It has been reported that paroxysmal a-fib induces atrial pressure and atrial volume expansion in canines under anesthesia [11]. Similarly, the a-fib observed in our patient is believed to have induced atrial volume expansion and, consequently, atrial wall distention, which would have led to a suppression of ADH and, thereby, caused diuresis. However, contrary to the mechanism of tachycardia-polyuria syndrome as it is currently understood, our patient had a higher-than-normal plasma ADH concentration.

ADH is known to regulate water absorption through the expression of aquaporin-2 on the V2 receptors of the collecting duct, and its production increases in response to increased plasma osmolality, reduced atrial pressure, and reduced intravascular volume [12]. Fuji et al. [8] reported that ADH may be increased to suppress water diuresis caused by supraventricular tachycardia, and that elevated ADH levels increased renal prostaglandin E2, thereby inducing natriuresis independently from ANP. Thus, the elevated ADH in our case seems to be a compensation mechanism to counteract the reduction of intravascular volume caused by polyuria, as opposed to being the cause of polyuria.

**Fig. 4.** This is atrial fibrillation occurred when swan-ganz catheter was re-inserted. ECG: electrocardiogram, ABP: arterial blood pressure.
ANP, which serves an essential role in tachycardia-polyuria syndrome, is a cardiac hormone secreted as a result of stretching of the atrial cardiocytes [13], and elevated atrial pressure is an important factor involved in its production [5]. ANP regulates the intravascular volume by blocking renin, angiotensin, and aldosterone secretion to induce natriuresis and diuresis [14]. Kinney et al. [2] reported that U/O is increased in tachycardia-polyuria syndrome as a result of natriuresis through sodium clearance, osmolar clearance, the ratio of sodium to osmolarity in urine (2 × urine sodium / urine osmolarity), and that sodium accounts for a high percentage of the excreted solutes. In the present case, U/A performed after the onset of tachycardia indicated natriuresis. This suggests that sodium excretion was the cause of the observed diuresis [2].

One hour after achieving a normal rhythm, test results confirmed that natriuresis was reduced and, consequently, ANP levels would have been lowered [4,5]. Further, an animal study revealed that atrial pressure increased by 81 ± 19% and atrial diameter by 21 ± 5% during a-fib [11]. Taken together, increased ANP seems to be the main mechanism of tachycardia and polyuria accompanied with natriuresis. However, the fact that we did not measure ANP concentration is a limitation to our report.

The Society of Cardiovascular Anesthesiologists/European Association of Cardiothoracic Anesthetists published a practice advisory for the management of perioperative a-fib in patients undergoing cardiac surgery, with several recommendations [15]. According to the practice advisory, perioperative a-fib should be treated with non-dihydropyridine calcium channel blockers or beta blockers (strength of recommendation = 1). If the patient is hemodynamically unstable, they should be treated with electrical or chemical (e.g., amiodarone) cardioversion (strength of recommendation = 1). If the patient is hemodynamically unstable, they should be treated with electrical or chemical (e.g., amiodarone) cardioversion (strength of recommendation = 1). Moreover, amiodarone is recommended (strength of recommendation = 2a) to prevent a-fib after cardiac surgery. However, when unresponsive tachycardia occurs, as in the present case, DC cardioversion may be necessary to achieve a normal sinus rhythm.

The present case highlighted the possibility that iatrogenic a-fib occurring during insertion of a swan-ganz catheter may cause polyuria. Polyuria during surgery has a great influence on the patient’s volume management. Therefore, an anesthesiologist must be familiar with the discrimination and treatment about perioperative polyuria. Notably, if atrial fibrillation is the cause of polyuria, DC cardioversion could be a way to stop polyuria if the drug does not respond.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article. This is a case report.

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REFERENCES

Tachycardia-polyuria syndrome


Hypertrophic osteoarthropathy (HOA) is a rare clinical condition including an abnormal periosteal reaction in the long bones that causes painful swelling and tenderness of the extremities, digital clubbing, arthritis, synovitis, and joint effusions [1]. Primary HOA is an autosomal dominant hereditary disease and represents only 3% of all cases [2]. Secondary HOA is predominantly associated with tumorous conditions and primarily with lung cancer [3]. HOA has been rarely reported in association with other cancers.

Case: A patient with a history of recurrent renal cell carcinoma was referred to our clinic with bilateral leg pain, knee joint effusion, and arthritis. Simple radiography and bone scintigraphy confirmed a diagnosis of HOA. Oral non-steroidal anti-inflammatory drugs, joint fluid aspiration, and intra-articular injection of pain medications were found to be effective in the management of HOA pain.

Conclusions: HOA prognosis depends on the underlying disease, therefore, cancer treatment is critical. This case demonstrates the need to consider HOA in patients with various malignancies who present with bone or joint pain of the extremities.

Keywords: Paraneoplastic syndrome; Periostitis; Renal cell carcinoma; Scintigraphy; Secondary hypertrophic osteoarthropathy.

Hypertrophic osteoarthropathy (HOA) is a rare clinical condition including an abnormal periosteal reaction in the long bones that causes painful swelling and tenderness of the extremities, digital clubbing, arthritis, synovitis, and joint effusions [1]. Primary HOA is an autosomal dominant hereditary disease and represents only 3% of all cases [2]. Secondary HOA is predominantly associated with tumorous conditions and primarily with lung cancer [3]. HOA has been rarely reported as a paraneoplastic syndrome associated with various malignancies including gastrointestinal, hematologic, nasopharyngeal, melanoma, breast, and renal cell cancer [3,4]. In one study, only two out of 30 patients presented with HOA caused by renal cell cancer (6.7%) [4].

Here, we review the diagnosis and treatment of an atypical case of HOA in a patient with recurrent renal cell cancer.

CASE REPORT

The patient was informed and has provided written consent for the publication of this case report.

A 53 year old man was referred to our pain clinic for painful bilateral lower leg swelling, which began 1 month earlier. On presentation, his pain severity was 6–8/10 on the visual analogue scale (VAS). He had a past medical history of renal cell carcinoma diagnosed 3 years ago and radical nephrectomy of the left kidney. After 1 year, he was found to have re-
current renal cell carcinoma and underwent chemotherapy. Moreover, he underwent a left hemicolectomy 1 year ago because of a metastatic lesion in the descending colon.

Physical exam revealed fluid shifting, tender swelling, and painful limitation of range of motion of both knees, suggesting joint effusion (Fig. 1). Digital clubbing was not present. To find the cause of the painful lower leg swelling, simple radiologic studies from the pelvis to the feet and whole body bone scintigraphy with Tc-99m hydroxymethylene diphosphonate were performed. Periosteal reactions were observed in both tibias, fibulas, and femurs on simple radiologic studies (Fig. 2). Bone scintigraphy revealed increased radiotracer uptake along the cortex of the appendicular bones (Fig. 3). Although the digital clubbing was not present, we could diagnose hypertrophic osteoarthropathy based on periosteal reactions found on X-rays and bone scintigraphy.

The patient was prescribed naproxen 1,000 mg/d for pain. An ultrasound guided therapeutic arthrocentesis of both knees was performed. Clear, yellowish joint fluid was aspirated from both knees (right 4 ml, left 12 ml). After the arthrocentesis, both knees were intra-articularly injected with

**Fig. 1.** Photographs of the patient’s legs. Bilateral swelling is observed from above the knees to the feet.

**Fig. 2.** Simple radiologic studies of the patient’s feet. A bilateral periosteal reaction indicates hypertrophic osteoarthropathy (arrows).
a mixture of 1 ml ropivacaine, 0.75 mg/ml; 2 ml sodium hyaluronate, 10 mg/ml; triamcinolone acetonide 10 mg; and morphine sulfate 0.5 mg.

At 1-week follow-up, the pain was greatly reduced from VAS 6–8/10 to 1–2/10. At the patient’s request, another ultrasound guided therapeutic arthrocentesis was performed, with 2 ml and 3 ml of joint fluid aspirated from the right and left knee, respectively. Subsequently, a mixture of 1 ml ropivacaine, 0.75 mg/ml; 2 ml sodium hyaluronate, 10 mg/ml; triamcinolone acetonide 10 mg; and morphine sulfate 1 mg was injected in each knee joint. The patient showed no side effects after arthrocentesis and injection.

The patient is undergoing chemotherapy for treatment of his renal cell cancer. Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended for pain control. At the last follow-up, four months since the original arthrocentesis, the patient reported his pain level as VAS 1–2/10.

DISCUSSION

HOA is a syndrome clinically characterized by abnormal skin and periosteal proliferation of the distal extremities [1]. Patients with HOA may be asymptomatic or present various clinical signs. The classical triad for HOA is digital clubbing, periostosis, and synovial effusions. Patients often present with periostosis, although not all patients have digital clubbing, joint pain, or effusion [5]. Patients may feel a burning sensation and bone pain as the disease progresses [1]. Clinical diagnosis may be challenging because the symptoms are similar to those of connective tissue diseases or inflammatory arthritis. In this case, the patient showed clinical signs of periostosis as pain and swelling of both legs and joint effusion of both knees but did not have clubbing of the fingers or toes.

The mechanism of pathogenesis of HOA is unclear. One possibility is a neurogenic pathway model. The vagus nerve innervates the organ with disease and induces a neural reflex that may cause vasodilation followed by increased blood flow to the extremities [6]. Another possibility is a humoral pathway. Hypoxia in patients with lung disease induces cytokines and growth factors such as vascular endothelial growth factor (VEGF), platelet-derived growth factor, and prostaglandin E2 (PGE2). These molecules induce development of new periosteal bone formation [7].

Primary HOA is a rare hereditary disease representing only 3% of all cases of HOA [2]. Also known as pachydermoperiostosis, it is characterized by early onset of clubbing and thickening of the skin of the face. Primary HOA involves mutations of the 15-hydroxyprostaglandin dehydrogenase gene and the solute carrier organic anion transporter family member 2A1 gene. Mutation of these genes impairs the ability to degrade PGE2. Elevation of PGE2 results in overexpression of VEGF. In consequence, excessive new bone formation appears by osteoblasts [8].

Secondary HOA is primarily associated with abnormal lung function because of lung cancer, interstitial lung disease, sarcoidosis, chronic obstructive pulmonary disease, pulmonary infections, abscess, empyema, or mesothelioma. Even with undamaged lungs, cyanotic heart disease can cause HOA by excluding the lungs from systemic circulation [1,3]. The most common cause of secondary HOA is non-

Fig. 3. Whole body bone scintigraphy. Increased radiotracer uptake is observed along the appendicular bone cortex.
small cell lung cancer. The incidence of HOA in lung cancer is reported as 4% to 17% [5]. It may appear as a generalized or localized form involving only one or two extremities. The generalized form is caused by systemic disease, while the localized form is associated with endothelial injury, such as arterial aneurysm, arterial graft infection, or a functioning arteriovenous fistula [9]. HOA has been rarely reported as a paraneoplastic syndrome in other malignancies including gastrointestinal, hematologic, nasopharyngeal, melanoma, breast, and renal cell cancer [3,4]. Renal cell cancer was the cause of HOA in this case.

Imaging evaluation can be a major tool for diagnosing HOA because serological tests are not reliable [3]. Plain radiographs are used as the first modality. Periostosis along the shaft of tubular bones is the key feature found on plain radiographs. The most commonly affected bones are the tibia, fibula, radius and ulna [3]. They may also present bony deformities and soft tissue swelling. Long standing clubbing can result in osseous resorptions of the fingers and toes. These bony changes appear first in the toes before they manifest in the fingers [1]. Joint involvement can also appear on plain radiographs as synovial effusions, joint space narrowing, erosions, or periarticular osteopenia [3].

Magnetic resonance imaging (MRI) can also be used to show periosteal reactions, osseous proliferation at the ligaments and tendons in later stages, and specific soft tissue changes in periarticular swelling sites. Also, MRI can be useful for identifying synovial effusion [3,10].

Bone scintigraphy is more sensitive for detecting HOA than radiography alone [11]. Patients with known malignancies are often found to have HOA on bone scintigraphy [3]. Significant radiotracer uptake is shown at the periosteum along the cortical margin of long tubular bones [12]. This modality can be used to estimate the response to therapy if findings resolve after treatment [13]. Similar to bone scintigraphy, positron emission tomography with 18F isotopes can also be used to show the hypermetabolic activity along the long tubular bones. In this case, periosteal reactions observed on simple radiologic studies and bone scintigraphy were diagnostic for HOA.

Radiological signs of periosteal reactions can appear in various conditions including thyroid acropachy, leukemia, lymphoma, hypervitaminosis A, venous stasis, and use of medications such as voriconazole. The type and distribution of periosteal reaction varies in these conditions. Bilaterally symmetrical involvement of the appendicular skeleton characterizes HOA [1,3]. Identifying underlying disease and reviewing medical history may help in patient diagnosis and treatment. In this case, the patient had known renal cell cancer, an absence of thyroid diseases, hematologic malignancies, or venous insufficiency, and no use of retinoids or voriconazole.

Because the prognosis and mortality of secondary HOA are associated with underlying disease, treatment should be focused on the primary disease, even considering surgical resection of the primary tumor. Symptomatic treatment options include analgesics, such as NSAIDs. In some cases, bisphosphonate and octreotide provided effective symptomatic treatment of bone pain [14]. Also, truncal vagotomy has shown symptomatic relief for refractory patients [15]. In this case, aspiration of knee joint fluid and intra-articular injection for pain were found to be effective. The patient is undergoing chemotherapy for the renal cell cancer after surgery on the primary and colon metastasis sites.

In summary, this case demonstrates that HOA should be considered in patients with malignancies other than lung cancer when they have bone or joint pain of the extremities, even without digital clubbing. Treating the underlying disease and pain management are both important. Pain management options in patients with HOA include analgesic medications such as NSAIDs, bisphosphonate, octreotide, surgery of the original tumor, and sympathectomy. As in this case, joint aspiration and intra-articular injection can be a treatment option for patients with joint effusions.

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

DATA AVAILABILITY STATEMENT
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS
Conceptualization: Hwa-Yong Shin. Writing - original draft: Kyung Seo Oh. Writing - review & editing: Kyung Seo Oh, Seung Young Lee, Hwa-Yong Shin. Supervision: Se-Hee Min, Choongun Ryu, Hwa-Yong Shin.
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Hypereosinophilic syndrome (HES) is characterized by an increase in the number of circulating eosinophils [1]. Patients with HES may present with various combinations of symptoms and signs of organ damage mediated by eosinophils, including dermatological, pulmonary, gastrointestinal, cardiac, and neurologic dysfunctions [2]. Four percent of all HES patients experience neurological manifestations, and peripheral polyneuropathy (PN) accounts for approximately half of these neurologic manifestations. Peripheral neuropathy can be classified into various types. For example, they can be symmetric or asymmetric, involve sensory nerves with or without involvement of motor nerves, and can cause mononeuritis multiplex or radiculopathy [3]. However, the pathophysiology of PN in patients with HES remains unclear. Therefore, there is no specific treatment for PN in patients with HES. Transcutaneous neurostimulatory treatment (TNT), of which scrambler therapy (ST) is the most well-known, has been used to treat chronic pain syndrome since 2003, when Marineo [4] suggested that ST was effective in patients with terminal cancer pain. The mechanism of TNT involves the production of 16 different electrical currents that stimulate normal nerve action potentials and replace “pain” with “non-pain” signals via noninvasive electrodes placed around the surface of painful areas [5]. This treatment has been utilized for the treatment of chronic intractable pain syndromes such as chemotherapy-induced neuropathy, postsurgical pain syndrome, or postherpetic neuralgia [6–8]. We recently experienced a case of successful treatment with Pain Block® (PB) (Koibig Inc., Korea) for TNT in a HES patient with peripheral polyneuropathy. Prior to
Writing informed consent was obtained from the patient for the publication of this case.

A 47-year-old female patient (height, 164 cm; and weight, 60 kg) visited our pain clinic for pain in both calves. She had been diagnosed with HES four years ago. She was referred from the hemato-oncology clinic because her pain was uncontrolled with pharmacological treatment, despite continuous treatment for a few years. She had no medical history except for HES and denied smoking or alcohol history. The degree of pain on the 1–10 numeric rating scale (NRS) was eight. She complained that she experienced several daily episodes of breakthrough pain increasing to NRS values of 9–10, and described the pain as a continuously tingling and stabbing pain. She did not have any motor weakness or paresthesia. Her Neuropathic Pain Scale (NPS) score was 61.0, and she had uncontrolled, severe neuropathic pain.

The location of the pain did not follow specific dermatomes, and it was expressed from both knees to the tip of the feet, entirely. Magnetic resonance imaging was performed to differentiate it from other diseases. However, she had only mild Achilles paratenonitis on both sides with no other specific lesions. Both calf muscle biopsies showed focal mixed inflammatory cell infiltration into the endomysium, forming inflamed granulation tissue with many eosinophils. At the first visit to our pain clinic, the patient had been administered oxycodone 5 mg bid, pregabalin 300 mg tid, acetaminophen 325 mg bid, tramadol 37.5 mg bid, and amitriptyline 10 mg qd. Tapentadol IR 50 mg was administered as rescue medication. However, she complained that the medication had an insufficient effect on her severe pain, and that she could not sleep very well at night. Therefore, we concluded that the patient needed additional treatment, and TNT was planned.

According to our hospital Institutional Review Board (IRB) regulation, Case report is not reviewed by IRB committee. As the patient’s pain was located below the knees, the PB electrodes were attached from both knees to the soles. (Figs. 1, 2) The detailed protocol is as follows: First, we clearly defined the area of pain on the patient before the start of TNT. Next, electrodes were attached to the areas proximal and distal to the margin of the area of pain. The PB was then turned on, and the electrode intensity was increased to the maximum tolerated intensity. Each session lasted for 40 min, and the entire treatment lasted for 15 consecutive sessions. However, a two-day interruption was considered acceptable. The dial of the PB can be adjusted from 0% to 100%. At the highest setting of 100% on the dial of PB, the amperage is 4.9–9.1 mA and the voltage is 7.4–13.8 V. In the case of this patient, a dial value of 35–50% was applied.

During PB treatment, the NRS score decreased to 0 or 1. The NRS score was maintained at 3 between visits to the pain clinic. The patient received a total of 15 sessions of PB treatment for five weeks. The area of pain did not decrease, but she reported disappearance of the breakthrough pain as well as NRS scores of 0 or 1 during treatment and 3 or 4 at home. Pharmacologic treatment was continued without a change in dosage but the patient did not take further rescue medication. The pain alleviation effect from the PB treatment continued for 2 months, during which breakthrough pain did not develop (Table 1). Her NPS score lowered to 16.0; however, during the third month after treatment, the pain recurred in the same area. She complained of an NRS
score of 6, which was lower than that before the initial treatment. She has been receiving the previous PB treatment again, and her NRS score has decreased to 2.

**DISCUSSION**

HES is a group of disorders marked by the sustained overproduction of eosinophils, in which eosinophilic infiltration and mediator release cause damage to multiple organs [9]. Blood eosinophilia is defined as an absolute eosinophil count of > $1.5 \times 10^9$/L, and HES is defined as a consistent blood eosinophilia and subsequent end organ dysfunction without evidence of an underlying cause. HES is initially treated with glucocorticoids. If the patient is steroid-unresponsive or has a special type of HES with Fip1-like 1-platelet-derived growth factor receptor alpha, imatinib mesylate may be administered [9,10].

In this case, TNT with PB is an effective treatment for PN induced by HES that does not respond to pharmacological treatment. HES is a very rare disease and its prevalence is not well known. In a study analyzing the database of the Surveillance, Epidemiology, and End Result program for cancer, the estimated prevalence was between 0.36–6.3 per 100,000 [11]. The mechanism by which PN appears in HES is still unclear, but it is thought that eosinophil deposition plays a major role in other complications and causes axonal degeneration with neurogenic atrophy of muscle [12]. As far as we know, there have been no reports on the specific treatment for PN induced by HES. Therefore, we suggest that the application of TNT could be expected to be effective, as in this case, where there are repetitive complaints or retractable PN despite pharmacological treatment.

Conventional treatments for peripheral polyneuropathy include pharmacologic treatment, such as anticonvulsants and antidepressants, and nerve blocks including central or peripheral nerve block. However, in this patient, pharmacologic treatment was not effective, and we did not consider nerve block because the patient’s symptoms did not follow a specific dermatome nor were they limited to the innervation area of a specific peripheral nerve. Although there have been no randomized controlled trials for the treatment of peripheral polyneuropathy, several studies have reported effective treatments for PN induced by chemotherapy or diabetes mellitus. As in our case, those studies showed that application of TNT to patients with PN was effective in relieving their pain, and they showed successful results during the application of TNT and in the follow-up period [13–15].

The mechanism underlying TNT is not clearly understood. According to Marineo [4], TNT provides “non-pain” information to the peripheral sensory nerve receptors, which is conveyed to the central nervous system through C-fibers and Aδ-fibers. Subsequently, it reduces pain [4,14]. Fig. 1 demonstrates the basic application of TNT in a patient. Before the first treatment with TNT, the pain area was clearly defined, and electrodes were attached to the areas proximal and distal to the margins of the pain area. Next, an electrical stimulus was applied, and the intensity was slowly increased until the patient could not tolerate the pain stimulation. Each treatment took approximately 40 min, and all consecutive sessions needed to be done approximately 10 to 15 times.

TNT differs from transcutaneous electrical nerve stimulation (TENS), which is usually used in physical therapy. TENS provides an on-off biphasic current without variation, whereas TNT provides continuously changing variable non-linear waveforms. In addition, the pulse rate of TNT is 43–52 Hz, and the mean energy delivered per second is generally less than that of standard TENS devices [6].

In TNT, ST is the representative choice ever since Marineo [4] first reported its application in a clinical situation. The PB used in this case is similar to ST at a pulse rate of 43–52 Hz. However, PB differs from ST in its pulse waveform. ST generates 16 specific types of waveforms, while PB generates a random waveform using a random variable program. This PB is a TNT product approved by the Korean Ministry of Food and Drug Safety for refractory pain, chronic pain, and cancer pain. Nevertheless, further prospective studies are needed.

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<th>Number of TNT</th>
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NRS: numeric rating scale, TNT: transcutaneous neurostimulatory treatment.

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Table 1. NRS Changes in the Patient

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required because the possible differences between the existing ST and PB in actual clinical situations are not yet known. We found TNT to be a clinically useful, non-invasive therapeutic modality. It should be considered as an effective alternative measure for treating PN induced by HES. Further studies including randomized controlled trials are needed to confirm and generalize our findings.

CONFLICTS OF INTEREST

In this case, the medical machine was provided as the hospital-based business program.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Venipuncture, or phlebotomy, is one of the most commonly performed minimally-invasive procedures, essential for routine blood sampling, intravenous fluid therapy, transfusion, and blood donation. Although this procedure is relatively harmless in most cases, it may be associated with a critical peripheral nerve injury such as complex regional pain syndrome (CRPS) [1,2].

A vein in the antecubital fossa is one of the first choices for routine blood sampling in adults. Specifically, the median cubital vein, located between the cephalic and basilic vein, is a large vein suitable for blood sampling. Other veins commonly used for blood sampling that are also located in the antecubital fossa include the cephalic vein, basilic vein, and median antebrachial vein [3]. However, the antecubital fossa is an anatomically complex area, in which the neurovascular structures may lie very close to each other, making the nerves vulnerable to injury during venipuncture. Moreover, the anatomical variations in the antecubital fossa between individuals add to the risk of nerve injury [4].

The incidence of nerve injury during venipuncture varies in different reports, ranging from 1/21,000–1/25,000 to as low as 1/67,000 [2,5,6]. While most of these patients fully recover, a rare possibility exists that they may experience severe, chronic pain that met the diagnostic criteria of CRPS.
Here, we present two self-reported cases of anesthesiologists experiencing nerve injury during blood sampling. Written consent for publication was obtained from the patients. We also discuss the importance of ultrasonography for the early diagnosis and prompt treatment of nerve injury following venipuncture.

**CASE REPORTS**

**Case 1**

A 28-year-old male patient undergoing venous blood sampling was punctured in the middle of the antecubital fossa of the left arm with a 21-gauge needle. During the procedure, he felt a sharp, electrical pain throughout his arm, extending from the venipuncture site to the tip of the fingers. The intensity of the pain was rated as 8/10 in the visual analog scale (VAS). After the needle was withdrawn, he experienced dysesthesia and burning pain in the anterior wrist and the anterior, lower half of his forearm, which was rated as 7–8/10 on the VAS and lasted for more than 24 h.

Since the pain and discomfort did not subside even after 24 h, he visited the pain clinic for evaluation and management. After a brief medical interview and physical examination to rule out peripheral neuropathy, ultrasonographic examination of the venipuncture site was performed to accurately assess the nerve. It revealed segmental swelling and perineural echogenic changes in the lateral antebrachial cutaneous branch of the musculocutaneous nerve at the forearm level (Fig. 1A), between the biceps brachii tendon and the punctured cephalic vein at the antecubital level, compared with contralateral side, suggestive of neuritis with perineural hemorrhage (Fig. 1B).

Low amplitudes in the left lateral and medial antebrachial cutaneous nerves were observed on a sensory nerve conduction study (NCS) performed on the same day, suggesting left lateral and medial antebrachial cutaneous neuropathy.

Consequently, a nerve block of the injured nerve was promptly performed on the same day. After local infiltration with 2% mepivacaine, a mixture of 0.75% ropivacaine (1 ml), triamcinolone (20 mg), and normal saline (2.5 ml) was injected around the nerve (Fig. 2). The patient experienced significant relief of pain and discomfort. Ultrasound-guided peripheral nerve block for the lateral antebrachial cutaneous nerve at the elbow. BnM: brachialis muscle, BT: biceps tendon, CV: cephalic vein, ECRL: extensor carpi radialis longus muscle, H: humerus, RN: radial nerve.
immediate pain relief, with no adverse effect. After the procedure, the patient reported a pain intensity of 1/10 on the VAS. Additionally, he was prescribed with prednisolone (5 mg), pregabalin (75 mg), tramadol (75 mg), acetaminophen (650 mg), and esomeprazole (20 mg) per os bis in die for a week.

The patient experienced an intermittent shooting, electrical pain (2–3/10 in the VAS) extending anteriorly from his forearm to his wrist for a week after administering the nerve block. The medications, including pregabalin (75 mg), naproxen (500 mg), and esomeprazole (20 mg) bis in die per os were prescribed for another week. In the following two weeks after the injury, his pain and discomfort gradually reduced to a degree that was ignorable.

A follow-up ultrasonographic examination at three weeks after the injury showed an improvement in the segmental swelling and perineural echogenic changes around the affected nerve, suggesting an improvement in the neuritis and perineural hemorrhage (Fig. 1C). The patient no longer experienced pain, discomfort, or paresthesia.

Case 2

A 32-year-old female patient was punctured with a 21-gauge needle in the middle of the antecubital fossa of the left arm for venous blood sampling. She felt an electrical sensation from her forearm to the tip of her fingers for a few seconds when her skin was punctured, followed by numbness after the needle was removed. Subsequently, she complained of a dysesthesia extending from her elbow to the tips of her first four fingers, and dull pain rated 7–8/10 on the VAS around the punctured area. She visited the pain clinic that afternoon.

Ultrasonographic examination of the antecubital area was performed to further evaluate the puncture site. Its results suggested probable injury of the lateral antebrachial cutaneous nerve, which lies adjacent to the median cubital vein, with mild surrounding infiltrates, as compared with the contralateral side. It showed similar ultrasonographic findings with Fig. 1A, B in Case 1.

After the ultrasonographic examination of the nerve injury, skin infiltration with 2% mepivacaine was performed and a nerve block of the injured nerve was performed with a mixture of 0.75% ropivacaine (1 ml), triamcinolone (20 mg), and normal saline (2.5 ml) was injected around the nerve. Immediately after the nerve block, her pain reduced to 1–2/10 on the VAS, with hypesthesia in the affected forearm. She was prescribed prednisolone (5 mg), pregabalin (75 mg), tramadol (37.5 mg), acetaminophen (325 mg), and esomeprazole (20 mg) per os bis in die for a week.

The pain around the puncture site worsened (6–7/10 in the VAS) 24 h after the nerve block, with further worsening through the following day (8/10 in the VAS). Following the administration of oral medication, the pain gradually subsided to 1–2/10 on the VAS over the course of a week.

The patient continued to experience intermittent shooting pain at the puncture site during arm movement, but without any sensory deficit. The oral medications, including pregabalin (75 mg), naproxen (500 mg), and esomeprazole (20 mg) per os bis in die were prescribed for another week. She had complete pain relief at 2 weeks after the injury without any tingling sensation and numbness.

Three and a half weeks later, a follow-up ultrasonographic examination was performed. Its results revealed a decreased extent of the echogenic lesion adjacent to the nerve in the left arm, which had been noted in the previous examination (similar findings with Fig. 1C). She was pain free, both at rest and with arm and hand movement.

DISCUSSION

This study is a report of two anesthesiologists’ self-reported cases of venipuncture-related nerve injury. They were able to describe the detailed clinical features of the condition from the doctor’s and the patient’s perspective throughout the course of the injury.

First and foremost, it is important to prevent nerve injury during venipuncture by carefully selecting the puncture site with the least risk of nerve injury. A typical venipuncture site is chosen among superficial veins in the antecubital fossa of the forearm. The lateral cutaneous nerve is seen deep along the cephalic vein in most cases. Risk of nerve damage is higher especially when the cephalic vein is punctured in the lower part of the cubital fossa, making it a dangerous area for venipuncture. The medial cutaneous nerve descends medial to the basilic vein, either passing over or under the ulnar portion of the median cubital vein. These anatomical relationships between veins and cutaneous nerves in the antebrachial fossa suggest that the radial side of median cubital vein is a relatively safe site for venipuncture [7,8]. Even with the safest puncture site, delicate maneuvering and careful handling of the needle or catheter is essential to avoid deep penetration, risking injuries of the nerve lying deep behind the vein. Additionally, multiple attempts in the
same site should be avoided.

Despite an appropriate and satisfactory venipuncture, a possibility of a nerve injury still exists. When venipuncture-related nerve injury is suspected, one should first elicit a history of recent venipuncture through history taking and physical examination, and rule out any underlying diseases that might cause peripheral neuropathy, such as diabetes. For a more accurate and objective diagnosis, other tools can be used, including electromyography (EMG), NCS, magnetic resonance imaging (MRI) and ultrasonography.

EMG and NCS are useful to localize and confirm peripheral nerve injuries [9]. Decreased conduction velocity or conduction block in the affected nerve on NCS is also indicative of nerve injury. However, electrodiagnostic studies cannot provide detailed information regarding the anatomy of the injured area or determine the severity of the injury, and the patients experience major discomfort during these studies.

MRI can also aid in assessing nerve injuries. It is helpful in directly evaluating the changes in the nerve signals and peripheral tissues, especially in the deeper structures that are hard to evaluate through ultrasound [9]. However, its expensive and time-consuming nature make MRI a less attractive diagnostic tool. In addition, MRI is contraindicated for some patients, including uncooperative children, patients with mechanical devices such as a pacemaker, or patients admitted to the intensive care unit.

Ultrasonography can be useful for localizing and diagnosing iatrogenic peripheral nerve injuries. Additionally, it can be used to assess the surrounding structures and detect abnormalities, such as hematoma. Doppler imaging can be used to assess the blood vessels and vascular changes in the area surrounding the injured nerve. Bedside ultrasonography is useful in the real-time assessment of nerve injuries, and can be performed in an acute phase of the injury without causing any pain to the patient, making it one of the most preferred tools for diagnosing peripheral nerve injury. Injection treatment can also be performed simultaneously with the diagnosis [10].

The first step in diagnosing an iatrogenic peripheral nerve injury through ultrasonography is identifying the lesion. A normal peripheral nerve is sheathed with an outer epineurium, which contains several fascicles composed of axons. A transducer should be placed at the nerve of interest at a 90-degree angle, and a cross sectional view of a normal peripheral nerve will show hyper-echoic epineurium with a few hypo-echoic fascicles within the epineurium. The peripheral nerve is further differentiated from the surrounding muscles and tendons, which are relatively more hypoechoic.

Once the nerve of interest is identified in a cross-sectional view, the probe should be moved along the nerve to scan the nerve throughout its course. Tracing the nerve of interest enables identifying any abnormalities in size and appearance, or discontinuation of the nerve. Turning the probe 90-degrees around can show a longitudinal image of the lesion. Longitudinal images can show changes in the nerve diameters or discontinuation of the nerves.

Ultrasonographic findings of a nerve injury include enlargement of nerve diameter indicating nerve swelling or neuroma, focal disorganization of its fascicular structure, or transection of the nerve. In a first-degree Sunderland nerve injury, or neurapraxia, the nerve retains its normal appearance with or without minor swelling of the nerve. A second-degree Sunderland nerve injury, or axonotmesis, shows a clearly enlarged diameter of the nerve due to axonal swelling and edema. Focal swelling and the surrounding edema can be shown with hyper-echogenicity. A third-degree or fourth-degree Sunderland nerve injury, or neurotmesis, shows loss of normal fascicular pattern due to involvement of the endoneurium. Hypo-echogenicity and marked enlargement of the nerve can also be noted. A fifth-degree Sunderland nerve injury is a complete transection of the nerve. In this kind of transection injury, ultrasound can detect discontinuation of the nerve, showing interruption of the epineurium and enlarged, hypo-echoic nerve stump. Distance between the lesion site, the affected muscles, and the skin can be measured and can help guide decision-making in treatment course.

Ultrasonic scanning of the lesion site can not only detect abnormalities of the nerve itself, but also reveal abnormalities in the surrounding areas. Such findings include scars, foreign bodies, or hematoma. Sharp scars associated with laceration with a knife or glass, needle or catheter related injury can be seen as hypoechoic, linear lines penetrating the skin, subcutaneous tissues, or interrupting nerve sheaths. Foreign bodies can be usually found as scattering sound-waves from their surfaces. A hematoma can be seen as a diffuse, hypo-echoic area on the image.

Diagnosis of iatrogenic nerve injury and identification of the lesion site should lead to prompt treatment. The initial general management of nerve injury is similar to that of other nerve lesions. Conservative management includes the administration of oral medications, including opioids, NSAIDs, adjuvant analgesics, such as gabapentin or pregabalin [11],...
and systemic glucocorticoids, along with physiotherapy to prevent atrophy of the muscles supplied by the affected nerve.

Additionally, immediate nerve blockade upon diagnosis of a nerve injury is crucial. A nerve block using local anesthetics is both a diagnostic and therapeutic tool for peripheral nerve injury. Nerve block can result in immediate pain relief of the affected area, which can confirm the diagnosis of a nerve injury and the location of the lesion site. Ultrasonography also serves as a superior tool for the peripheral nerve block [12].

With the probe in the exact lesion site, the practitioner should carefully puncture the skin near the affected area. The needle tip should be visible while the needle is advanced, until the tip is placed desirably around the injured nerve. Pre-measured local anesthetics are injected through the needle and infiltrate around the injured nerve, which can be observed in real-time with the help of ultrasonography. Because the course of the needle is visible at all times, it is possible for the practitioner to avoid other nearby structures. Thus, the use of ultrasonography results in fewer complications with a shorter performance time. Local glucocorticoid injection is also used to inhibit the release of local inflammatory mediators and decrease ectopic neuronal discharges [13], aiding in a quicker recovery time.

Needle or catheter related nerve injury may also occur during the administration of regional anesthesia, such as brachial plexus block [14], or under general anesthesia. Central venous catheterization is among one of the most commonly performed catheterization procedures under general anesthesia. The incidence of nerve injury during subclavian central venous catheterization has been reported as 0.6% [15]. Such catheter related nerve injuries during procedures under regional or general anesthesia can be prevented by the routine application of ultrasound during these procedures. The practitioner can avoid nerve injuries by carefully inspecting the vein that is to be cannulated and its surrounding structures.

In conclusion, it is crucial to avoid nerve injury during venipuncture or catheter related procedures in the first place by carefully selecting the puncture site as well as the using ultrasonography for procedures with a risk of nerve injury. Furthermore, it is important for both the practitioner and the patient to be aware of the possibility of nerve injury during seemingly harmless procedures, such as venipuncture for routine blood sampling. When a peripheral nerve injury is suspected despite many efforts, application of ultrasonography for the early detection and prompt diagnosis of nerve injury during needle or catheter related procedures as well as immediate nerve block of the affected nerve are of utmost importance in alleviating pain and shortening the course of the injury.

**CONFLICTS OF INTEREST**

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

**DATA AVAILABILITY STATEMENT**

All data generated or analyzed during this study are included in this published article. This is a case report.

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The correlation between the STOP-Bang score and oxygen saturation during spinal anesthesia with dexmedetomidine sedation

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INTRODUCTION

For regional anesthesia, sedation is widely used for patient comfort and is required in several places in the hospital as well as in the operating room [1]. Dexmedetomidine has a lesser effect on the respiratory system than other sedative drugs such as propofol or benzodiazepines, especially for short-term sedation such as for drug-induced sleep endoscopy [2,3]. However, studies have shown that central sleep apnea does not occur, but obstructive sleep apnea (OSA) may worsen [4]. Of the complications related to sedation, airway obstruction can cause hypoventilation and hypoxia [5]. If hypoxia persists during surgery, stable sedation will be impossible, and the patient may wake up during the procedure, which may cause an interruption or necessitate unintended discontinuation [6].

Background: The STOP-Bang questionnaire is a simple screening tool with high sensitivity for the detection of severe obstructive sleep apnea. Predicting airway obstruction would allow the safe management of sedative patients to prevent intraoperative hypoxia. This study was designed to check the correlation between the STOP-Bang score and oxygen saturation (SpO₂) during sedation and confirm the availability of the STOP-Bang questionnaire as a preoperative exam for predicting the incidence of hypoxia in sedative patient management.

Methods: This study included 56 patients who received spinal anesthesia. The pre-anesthesia evaluation was conducted using the STOP-Bang questionnaire. The patients were under spinal anesthesia with an average block level of T10. Dexmedetomidine was infused with a loading dose of 1 µg/kg over 10 min and a maintenance dose of 0.5 µg/kg/h until the end of the procedure. The SpO₂ of the patients was recorded every 5 min.

Results: The STOP-Bang score was negatively correlated with the lowest SpO₂ (coefficient = −0.774, 95% confidence interval [CI]: −0.855 to −0.649, standard error [SE] = 0.054, P < 0.001). The item of “observed apnea” was the most correlated one with hypoxic events (odds ratio = 6.00, 95% CI: 1.086 to 33.145).

Conclusions: The STOP-Bang score was significantly correlated with the lowest SpO₂ during spinal anesthesia, which enabled the prediction of meaningful hypoxia before it occurred in the sedated patients.

Keywords: Dexmedetomidine; Hypoxia; Obstructive sleep apnea; Sedation.
In this regard, OSA is the most common sleep disorder, mainly due to upper respiratory tract obstruction with a prevalence of 10% in men and 3% in women aged between 30 and 49 years, and approximately 17% of men and 9% of women aged between 50 and 70 years. The incidence of hypoxemia in patients at risk for OSA is high [7]. Likewise, the incidence of difficult mask ventilation or difficult intubation is high [8]. Polysomnography, the standard method for diagnosing OSA, is not time- and cost-effective to apply to all patients for preoperative risk evaluation of OSA.

The STOP-Bang questionnaire uses only eight items to calculate the risk of OSA. The eight items include the patient’s body mass index (BMI, gender, age, neck circumference, hypertension under treatment, daily drowsiness, snoring, and apnea during sleep [9,10]. It does not require such a long time, and patients feel more comfortable with it. Although it seems simple compared with other screening tools, its sensitivity is sufficiently high to be reliable in clinical fields [11]. Therefore, the STOP-Bang questionnaire, which has the advantages of simple questions and high sensitivity over other OSA screening tools [12,13], was used for this study to identify patients at high-risk of hypoxemia before sedation.

The authors hypothesized that the STOP-Bang score would be correlated with the incidence of hypoxic events during sedation in patients undergoing spinal anesthesia. The STOP-Bang score can be used to predict the degree of desaturation in sedated patients.

The primary outcome of the study was to check the correlation between the STOP-Bang score and oxygen saturation during dexmedetomidine sedation. Additional attempts were made to determine the cut-off value of the STOP-Bang score that can predict hypoxia during sedation and the items with the highest diagnostic values.

**MATERIALS AND METHODS**

**Study sample**

This study was approved by the Institutional Review Board (no. KUGH 2019-11-032). Preoperative screening of orthopedic and urological patients who underwent sedation with dexmedetomidine after spinal anesthesia was performed. The exclusion criteria were as follows: American Society of Anesthesiologists physical status class of ≥ 3, lateral decubitus or prone positioning during surgery, problems of the upper respiratory tract, history of severe asthma or chronic obstructive lung disease, refusal of intraoperative sedation, or sensory block higher than T5. Patients with American Society of Anesthesiologists physical status class 3 due to a high BMI value of > 40 kg/m² without any other underlying diseases were included for consideration of the purpose of the study. Written informed consent was obtained from all the patients.

The STOP-Bang score of the patient was confirmed through pre-anesthesia evaluation. The STOP-Bang questionnaire consists of four questions and four clinical characteristics. The STOP-Bang score ranged from 0 to 8 points based on eight items (Supplementary Figs. 1, 2; S = Snoring; T = Tiredness; O = Observed apnea; P = Being treated for high blood pressure; B = BMI over 35 kg/m²; A = age over 50 years; N = neck circumference over 43 cm in males and 41 cm in females; G = gender of males). Patients were classified based on the STOP-Bang questionnaire scores into three groups: the high-risk, intermediate-risk, and low-risk of OSA groups (low-risk group, 0–2 points; intermediate-risk group, 3–4 points; high-risk group, 5–8 points or 2–4 points of STOP questions with at least one of B, N, and G). The official STOP-Bang questionnaire format was used in the design of the study; however, to be considerate of patients, an official Korean translation version was used when surveying the patients. Both forms were provided at www.STOPBANG.ca by Chung et al. [13].

**Spinal anesthesia and patient sedation**

The patients were placed in the right or left lateral position for spinal anesthesia while monitoring their noninvasive blood pressure, electrocardiogram, and pulse saturation. After disinfection of the skin with povidone-iodine solution, a 25-gauge spinal needle was used in a median approach between the 3rd and 4th or the 4th and 5th lumbar spinous process while checking the free flow of cerebrospinal fluid, and a heavy bupivacaine 10–12 mg was injected. Immediately after the removal of the spinal needle, the patient was placed in the supine position and waited for approximately 10 minutes to check the sensory block height using the pinprick test. Dexmedetomidine was used for patient sedation during the surgery with a loading dose of 1 μg/kg for 10 min followed by a maintenance dose at a rate not exceeding 0.5 μg/kg/h until the end of the surgery. During dexmedetomidine sedation, vital signs, including SpO₂, were measured and recorded at 5-min intervals. End-tidal capnography was used to confirm the apnea
during sedation. The oxygen mask was applied immediately to the patient when the SpO₂ during sedation decreased to 92% and lasted more than 30 s or rapidly decreased to 90% or less. In such cases, maintenance dose adjustment and adequate stimulation to wake up the patient were provided, if necessary. Rescue steps, such as jaw thrust or manual ventilation, were planned as needed.

Statistical analysis

According to a previous study by Oshita et al. [14] and the pilot data from our center, we assumed that the correlation between the STOP-Bang score and the lowest SpO₂ was 0.4 in calculating sample size. Assuming an attrition rate of 10%, a sample size of 51 patients were determined to be an adequate sample size to aim for 80% power and 5% type-1 error.

All statistical analyses were performed using IBM SPSS version 20.0 (IBM Co., USA). The correlation between the lowest SpO₂ and the STOP-Bang scores, age, and BMI were analyzed using simple linear regression and multiple linear regression analysis. The receiver operating characteristic (ROC) curve and the area under the curve (AUC) values were calculated to determine the diagnostic usefulness of hypoxic events and the cut-off value of the STOP-Bang score, age, and BMI. The Mann–Whitney U test and the chi-square test were used to compare the age and BMI of the hypoxic and non-hypoxic groups. The correlations between the individual items of the STOP-Bang questionnaire and the hypoxic events were also analyzed with odds ratios and 95% confidence intervals (CI). Two-sided P values of < 0.05 represented statistical significance.

RESULTS

From February 2020 to May 2020, 60 patients were enrolled in the present study. Four patients dropped out due to conversion from spinal anesthesia to general anesthesia (Fig. 1). The patient characteristics, level of spinal block, sedation time, and the STOP-Bang questionnaire composition ratio are summarized in Table 1.

A negative correlation (coefficient = −0.774, 95% CI: −0.855 to −0.649, standard error [SE] = 0.054, P < 0.001) between the STOP-Bang score and the lowest SpO₂ value was observed (Table 2). In addition to the STOP-Bang score, age and BMI, which are expected to be associated with hypoxia during sedation, were also evaluated using Spearman cor-
relation analysis. Compared with the STOP-Bang score, BMI was weakly correlated with the lowest SpO₂ (coefficient = –0.288, 95% CI: –0.518 to –0.013, SE = 0.142, P = 0.031) and age had no correlation with the lowest SpO₂ (coefficients = –0.201, 95% CI: –0.418 to 0.032, SE = 0.114, P = 0.137). Scatter plots of the lowest oxygen saturation during sedation and the STOP-Bang score, age, and BMI are shown in Fig. 2.

The ROC analysis of the STOP-Bang score, age, and BMI was performed to determine their usefulness in predicting hypoxic events during sedation. Unlike age and BMI, only the STOP-Bang score was statistically significant (AUC = 0.943, 95% CI: 0.884 to 1.000, P < 0.001) as a diagnostic tool for hypoxia. The cut-off value of the STOP-Bang score was 4.

Among 8 items of the STOP-Bang questionnaire, 6 items of STOP were analyzed using odds ratio, and the item of “observed apnea” turned out to be the most correlated one with hypoxic events (Table 3). None of the patients had a BMI of > 35 kg/m². Only one patient was included in the neck circumference section. Therefore, a statistical analysis of both items was not possible.

Oxygen masks were immediately applied to eight patients due to intraoperative SpO₂ of < 92% lasting for more than 30 s or a sudden decrease in saturation to less than 90% (Table 4). In addition, three patients showed mild bradycardia and were administered glycopyrrolate. After glycopyrrolate injection and a reduction in the dexmedetomidine maintenance dose, the heart rate recovered.

**DISCUSSION**

Respiratory depression is a common problem associated with sedation. Dexmedetomidine, a selective α₂ adrenergic receptor agonist, has sedative and analgesic properties. Its sedation is similar to that of natural sleep; therefore, it is known to cause less respiratory depression [15]. However, the advantage of being similar to natural sleep implies that

![Fig. 2. Scatter plots of lowest oxygen saturation during sedation and various patient factors. The results are shown for (A) STOP-Bang score (B) Age (C) Body mass index. BMI: body mass index.](image)

| Table 2. Spearman Correlation Analysis of Lowest SpO₂ and STOP-Bang Score, Age, and BMI |
|------------------------------------|----------------|----------------|--------|------|
| Items                              | Coefficient   | 95% CI for B   | SE     | P value |
| STOP-Bang score                    | –0.774        | –0.855 to –0.649 | 0.054  | < 0.001 |
| Age                                | –0.201        | –0.418 to 0.032 | 0.117  | 0.137  |
| BMI                                | –0.288        | –0.518 to –0.013 | 0.142  | 0.031  |

CI: confidence interval, SE: standard error of coefficient B, BMI: body mass index.

<table>
<thead>
<tr>
<th>Table 3. Odds Ratios of STOP-Bang Questionnaire Items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questionnaire</td>
</tr>
<tr>
<td>Snoring</td>
</tr>
<tr>
<td>Tired</td>
</tr>
<tr>
<td>Observed</td>
</tr>
<tr>
<td>Pressure</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Gender</td>
</tr>
</tbody>
</table>

CI: confidence interval. *P value < 0.05.
the incidence rate of OSA is high, as reported by Shin et al. [16]. OSA has a causal relationship with hypoxia during sedation, and severe hypoxia may be associated with increased mortality and morbidity [6]. Predicting those who are more likely to experience hypoxia will help us prepare for hypoxia during sedation.

The Berlin questionnaire, the STOP-Bang questionnaire, and the Epworth sleepiness scale are widely used as OSA screening tools. Among them, the STOP-Bang questionnaire is relatively accurate with high sensitivity and can be used for the early diagnosis of OSA, even in an environment where polysomnography is difficult to perform [17]. In addition, the STOP-Bang questionnaire uses only eight items to calculate the risk of OSA. The eight items include BMI, gender, age, neck circumference, hypertension under treatment, daily drowsiness, snoring, and apnea during sleep [9, 10]. Therefore, the STOP-Bang score was selected as an index correlated with SpO2 in relation to hypoxia during sedation, since all items can be easily confirmed in advance with preoperative anesthesia evaluation without additional monitoring devices.

As a result, the STOP-Bang score and the lowest SpO2 showed a negative correlation (coefficient = −0.774, 95% CI: −0.855 to −0.649, SE = 0.054, P < 0.001). Although there were age and BMI items in the STOP-Bang questionnaire, weak interactions were observed between oxygen saturation and actual age or BMI. The reason for this low correlation is thought to be the binary classification of these items, such as age of 50 years or older and BMI above 35 kg/m².

Hypoxic events occurred in eight patients, hypoxia was resolved in two patients by supplying oxygen through a simple mask, but the other 6 patients resolved hypoxia through jaw thrust or manual ventilation. In 4 of these cases, the dexmedetomidine infusion rate was adjusted to half. This result is thought to have been influenced by their relatively high ages. The mean age of the hypoxic event group (69.5 ± 6.6) was higher than that of the group without events (59.8 ± 15.3).

ROC analysis was performed to check whether the STOP-Bang score is valid as a diagnostic tool for predicting hypoxia (Fig. 3). Consequently, the STOP-Bang score showed a stronger association with hypoxic events than the age and BMI of the patients. The cut-off value of the STOP-Bang score for predicting hypoxic events was 4 points. Previous studies by Chung et al. [13] showed a cut-off value of 3 points for the STOP-Bang score. This may be a result of the differences in the average BMI and the average neck circumference, proba-

### Table 4. Patients Who Experienced Hypoxic Events (n = 8)

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>BMI (kg/m²)</th>
<th>STOP-Bang score</th>
<th>Risk</th>
<th>Lowest SpO₂ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>64</td>
<td>M</td>
<td>22.1</td>
<td>5</td>
<td>High</td>
<td>81</td>
</tr>
<tr>
<td>12</td>
<td>81</td>
<td>M</td>
<td>24.5</td>
<td>5</td>
<td>High</td>
<td>88</td>
</tr>
<tr>
<td>22</td>
<td>70</td>
<td>M</td>
<td>27.2</td>
<td>5</td>
<td>High</td>
<td>88</td>
</tr>
<tr>
<td>23</td>
<td>64</td>
<td>F</td>
<td>22.3</td>
<td>4</td>
<td>Intermediate</td>
<td>86</td>
</tr>
<tr>
<td>35</td>
<td>71</td>
<td>M</td>
<td>25.0</td>
<td>5</td>
<td>High</td>
<td>88</td>
</tr>
<tr>
<td>46</td>
<td>67</td>
<td>M</td>
<td>30.1</td>
<td>4</td>
<td>High</td>
<td>88</td>
</tr>
<tr>
<td>47</td>
<td>62</td>
<td>F</td>
<td>22.8</td>
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<td>85</td>
</tr>
<tr>
<td>55</td>
<td>64</td>
<td>M</td>
<td>29.7</td>
<td>4</td>
<td>High</td>
<td>84</td>
</tr>
</tbody>
</table>

Values are expressed as numbers.

![Fig. 3. Receiver operating characteristic curves and area under the curve (AUC) for STOP-Bang score, age, and body mass index (BMI).](www.anesth-pain-med.org)
bly due to the nationality of the patient sample. The item “B” did not apply to any patient, and item “N” applied to only one patient. In this study, the cut-off value of the BMI was 27. According to the Asia-Pacific obesity diagnosis standards, obesity is defined as a BMI of > 25, and high obesity is defined as a BMI of > 30. It seems that the standard points for BMI and neck circumference for the STOP-Bang questionnaire are quite high for most Korean patients. This is considered the reason for the maximum STOP-Bang score of 5 in this study.

In the odds ratio analysis for 8 individual items, the “Snoring,” “Observed,” and “Pressure” items were statistically significant. In particular, the “Observed” item showed a very high odds ratio of 6.0, compared with those of the other two items, which were nearly 1.4. Although it usually refers to observation by non-medical personnel, this result is consistent with the intuition that the “Observed” item is highly correlated with OSA, and similar reports have been made in studies such as Neves Junior et al. [18].

The limitation of this study was that the oxygen mask with airway adjustments was immediately applied for patient safety when the SpO2 decreased to 92% and lasted more than 30 s or rapidly decreased to less than 90%. Therefore, it was not possible to accurately evaluate the reduction in SpO2 in the high-risk group. In addition, since there is a part in which the patients answer the questions themselves, it is difficult to calculate the correct score if there is an incorrect answer from the patient, whether intended or not.

The duration for the lowest SpO2 was not directly collected, and the times of occurrence could not be analyzed. The 5-min interval recording system did not reflect the saturation in real-time, and it was impossible to collect retrospective data. However, according to the author’s experience, most cases of hypoxia occurred nearly immediately after the loading dose was fully administered. There may be bias due to oxygen supply, and further research is needed.

In conclusion, we confirmed that the STOP-Bang was correlated with SpO2 in patients undergoing dexmedetomidine sedation in this study. This study proposes the use of the STOP-Bang score for preoperative evaluation and sedation management. The addition of the “observed” item for the pre-anesthesia evaluation may also be helpful.

SUPPLEMENTARY MATERIALS

Supplementary data including a STOP-Bang questionnaire can be found online at https://doi.org/10.17085/apm.21011.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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REFERENCES


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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 Running title
      A running title of no more than 40 characters, including letters and spaces in Korean, or 10 words in English, should be provided. If this title is inappropriate, the Editorial Board may revise it.
      Ex) Kim et al. [1]
   ③ Author information
      First name, middle initial, and last name of each author, with their highest academic degree(s) (M.D., Ph.D., etc.), and institutional affiliations; make sure the names of and the order of authors as they appear on the Title Page and entered in the system match exactly.
   ④ Previous presentation in conferences
      Title of the conference, date of presentation, and the location of the conference may be described.
   ⑤ Funding statement
      Disclosure of all financial support for the work, including departmental or institutional funding/support.
   ⑥ Conflicts of interest
      Any conflicts of interest for any or all authors within the 36 months of submission. If no competing interests, please add the following statement: “The authors declare no competing interests.” If any of these elements are not applicable to your submission, write “not applicable” after the number and topic; for example, “Prior Presentations: Not applicable.”
   ② Manuscript
      ① Title and Running title (without author information)
         It should be the same as the Cover page.
      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 key words 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.

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

4 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 cmH_2O 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], Mg^{2+}[O], Mg^{2+}[×], Mg^{2+}[×]
  Ex) Premedicated magnesium [O]
  Ex) Premedicated Mg^{2+}[O]

5 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.
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, end-point. 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/m^2 should be expressed as 2.42 (0.31) L/min/m^2.

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.

Figures and Photographs

① APM encourages authors to use color to increase the clarity of figures. Please note that color figures are used without charge.

② 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.

③ 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).

④ 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.

⑤ In horizontal and vertical legends, the letter of the first English word should be capitalized.

⑥ Connections between numbers should be denoted by “−”, not “–”. Do not space the numbers (ex. 2–4).

⑦ 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.

⑧ Pathological samples should be pictured with a measuring stick.

Video (movie) clip(s)

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

① 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.

② 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.

③ Video clips are uploaded as the last file(s) at the time of manuscript submission and should be marked as supplementary video files.

④ 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).

⑤ The maximum number of video clips is 20.

⑥ 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.

⑦ 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.

⑧ Supplemental still images that correspond to the re-
pective 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.