The influence of propofol and sevoflurane on hemostasis: a rotational thromboelastographic study

Bon-Wook Koo, Hyo-Seok Na, Young-Tae Jeon, Jung-Won Hwang, and Sang-Hwan Do

Background: Using rotational thromboelastometry (ROTEM) analysis, we investigated the difference in blood hemostasis, based on the primary anesthetic agents used during general anesthesia.

Methods: Sixty-six adult patients scheduled for elective ophthalmic surgery under general anesthesia were evaluated with regard to changes in each parameter in INTEM, EXTEM, and FIBTEM analyses. The patients received intravenous anesthesia with propofol and remifentanil (TIVA group) or inhalation anesthesia with sevoflurane (SEVO group). The ROTEM tests were performed 10 min before starting anesthesia and 1 h after finishing anesthesia. The INTEM and EXTEM analyses included the clotting time (CT), clot firmness time (CFT), alpha angle (α), and maximum clot firmness (MCF). The FIBTEM analyzed only MCF. Maximum clot elasticity (MCE) was calculated by \((MCF \times 100)/(100 - MCF)\). The platelet component of clot strength was calculated as follows: \(MCE_{\text{platelet}} = MCE_{\text{EXTEM}} - MCE_{\text{FIBTEM}}\).

Results: The preoperative and postoperative parameters (CT, CFT, α, and MCF) in the INTEM, EXTEM, and FIBTEM analyses were not significantly different between the two groups. The \(MCE_{\text{platelet}}\) also did not show a significant difference.

Conclusions: Presuming that the ophthalmic surgery had a minimal traumatic effect, we conclude that both anesthetic agents cause negligible changes in ROTEM analyses postoperatively. (Anesth Pain Med 2014; 9: 292-297)

Key Words: Hemostasis, Propofol, Rotational thromboelastometry, Sevoflurane.

INTRODUCTION

Various anesthetic agents are administered for general anesthesia. Inhalation anesthetic gas or propofol is commonly used to maintain general anesthesia. Several studies have investigated the effect of anesthetic agents on hemostasis; however, the results still remain inconclusive. Only halothane was proved to inhibit platelet aggregation in vivo and in vitro [1], which is no longer used in clinical situations. Mizobe reported that propofol inhibited platelet aggregation and suppressed calcium mobilization, and sevoflurane could inhibit platelet aggregation induced by weak agonist [2]. In a previous study performed in endoscopic sinus surgery, both sevoflurane and propofol showed the impairment of platelet function on 45 min after surgery with comparable blood loss and endoscopic surgical vision; however, the primary hemostasis was more affected in propofol anesthesia [3]. Similarly, Yuki et al. [4] proved that isoflurane and sevoflurane impaired the activation of \(\alpha_{IIb}\beta_{3}\), activation of which plays a key role in platelet aggregation and clot stabilization. On the contrary, another study demonstrated that platelet function and fibrinolysis were unaltered during propofol or sevoflurane anesthesia in tympanoplasty surgery [5].

Those studies analyzed in vitro the aggregation ratio, platelet function test, or laboratory examinations, such as prothrombin time (PT), activated partial thromboplastin time (aPTT), antithrombin III, fibrinogen, and D-dimer. By contrast, rotational thromboelastometry (ROTEM) is able to provide a complete view of hemostasis, screen the blood coagulable state, and calculate the contribution of platelet component through the whole blood analysis [6]. Because platelet plug formation, coagulation cascade activation, and fibrin polymerization simultaneously participate in hemostasis, ROTEM analysis can provide more optimal results relevant to clinical hemostasis without complicated blood sample preparation.

During surgery, tissue trauma by surgical manipulation increases the levels of coagulation factors [7,8], and leads to platelet aggregation and blood hypercoagulability by releasing stress hormones, such as catecholamines, cortisol, and glucagon.
[9]. For the purpose of eliminating the surgical effect on hemostasis, we conducted this clinical study in ophthalmic surgery under general anesthesia. By using ROTEM analysis in this study, we investigated the hemostatic differences based on the primary anesthetic agents under the hypothesis that propofol-based anesthesia would impair postoperative hemostasis more than sevoflurane-based anesthesia.

MATERIALS AND METHODS

The Institutional Review Board provided approval for the study, and written informed consent was obtained from all patients scheduled for ophthalmic surgery under general anesthesia. Eligible patients were American Society of Anesthesiologist physical status I or II, and the preoperative exclusion criteria were hematologic disorders, severe anemia, liver disease, kidney disease, or the use of a medication that interferes with hemostasis.

One anesthetic care provider randomly allocated the enrolled patients to the TIVA group or the SEVO group by extracting a sealed envelope before starting anesthesia. The patients were not informed of the group to which they had been allocated. The TIVA group received propofol and remifentanil, and the SEVO group received sevoflurane as main anesthetic agents for general anesthesia.

In the operating room, standard monitoring was established, which included pulse oximetry, electrocardiography, and non-invasive blood pressure monitoring. The bispectral index (BIS) was only monitored in patients assigned to the TIVA group.

In the TIVA group, propofol and remifentanil were administered by a target-controlled infusion device (Orchestra; Fresenius Kabi, Brezins, France) at effect site concentration of 4 μg/ml and 4 ng/ml, respectively. After confirming loss of consciousness, 0.6 mg/kg of rocuronium was administered to obtain neuromuscular block for tracheal intubation. After tracheal intubation, the patient’s lungs were ventilated with 50% oxygen in medical air. Anesthesia was maintained by a continuous infusion of propofol and remifentanil. The effect site concentration of propofol was adjusted to maintain the BIS value in the range of 40-50. Remifentanil was titrated by 1 ng/ml based on the patient’s hemodynamic measurements, which were maintained within 20% of their respective pre-anesthetic values.

In the SEVO group, anesthesia was induced with thiopental sodium (5 mg/kg), alfentanil (10 μg/kg), rocuronium (0.6 mg/kg), and 8% sevoflurane in 100% oxygen. Anesthesia was then maintained with sevoflurane and 50% oxygen in medical air. The sevoflurane concentration was adjusted, based on the hemodynamic measurements. To maintain arterial pressure and heart rate changes within 20% of the preoperative value, sevoflurane was increased or decreased by 1%.

In both groups, 5 mg of ephedrine was administered if the systolic arterial pressure decreased to less than 80% of the pre-anesthetic value. When the heart rate decreased below 45 beats/min, the patients received 0.5 mg of atropine. At the end of surgery, propofol, remifentanil, or sevoflurane were discontinued. Glycopyrrolate (0.01 mg/kg) and neostigmine (0.04 mg/kg) were administered to aid the recovery from the neuromuscular blockade. Manual ventilation was performed using 100% oxygen until the patient recovered spontaneous ventilation. After the patients were extubated, they were transferred to the post-anesthetic care unit.

One outcome assessor, who did not know the patients’ group assignment, obtained the patients’ blood samples from their antecubital vein at 10 min before the induction of anesthesia and at postoperative 1 h. Using two syringes, 5 ml of blood was discarded initially, and then another 3 ml of venous blood was obtained with minimal stasis. For the thromboelastometry analysis, the blood sample was placed into citrate-containing BD vacutainer tubes (Becton, Dickinson and Company, Franklin Lakes, NJ, USA).

Within 10 min after obtaining the blood sample, thromboelastometry was analyzed automatically by the ROTEM© Coagulation Analyzer (Tem International GmbH, Munich, Germany). We ran three ROTEM tests: INTEG, EXTEM, and FIBTEM. INTEM and EXTEM make fast assessment of clot formation, fibrin polymerization, and fibrinolysis through the intrinsic and extrinsic pathway, respectively. FIBTEM conduct qualitative assessment of fibrinogen status without platelet component. The following variables were measured: clotting time (CT), clot formation time (CFT), alpha angle (α), and maximum clot firmness (MCF) for the INTEM and EXTEM assays, and MCF for the FIBTEM assay. Maximum clot elasticity (MCE) for the actual physical properties of clot strength was calculated as follows: $MCE = (MCF \times 100) \div (100 - MCF)$. The platelet component of clot strength was calculated by $MCE_{\text{platelet}} = MCE_{\text{EXTEM}} - MCE_{\text{FIBTEM}}$ [10].

The primary outcomes were the results of the INTEM, EXTEM, and FIBTEM variables, and the calculated MCE. The secondary outcomes included the preoperative hemoglobin level, platelets count, international normalized ratio of prothrombin.
Fig. 1. Flow chart of the patients’ enrollment.

The values are presented as the mean ± SD or by the number (%). DCR: dacryocystorhinostomy, IOL: intraocular lens, NLD: nasolacrimal duct, PCL: posterior chamber lens, PE: phacoemulsification, PKP: penetrating keratoplasty, SO: silicon oil.
which showed no statistical difference (P > 0.05). The preoperative hemoglobin levels, platelets count, PT-INR, aPTT, and fibrinogen levels were comparable in both groups (P > 0.05) (Table 2).

Preoperative and postoperative parameters of the INTEM, EXTEM, and FIBTEM assays were not significantly different between the TIVA and SEVO groups (P > 0.05). The postoperative ROTEM values also showed no significant changes, compared to the preoperative values in each group (P > 0.05) (Table 3).

The pre- and postoperative MCE\textsubscript{EXTEM} and MCE\textsubscript{FIBTEM} were comparable between the two groups (P > 0.05) (Fig. 2). The preoperative MCE\textsubscript{platelet} values did not show a significant difference (126.0 ± 22.6 in TIVA group vs. 127.8 ± 25.7 in SEVO group, P > 0.05), and the postoperative MCE\textsubscript{platelet} of two groups also had no statistical significance (123.4 ± 33.8 in TIVA group vs. 133.9 ± 24.3 in SEVO group, P > 0.05) (Fig. 2).

### DISCUSSION

This study investigated the effect of different anesthetic agents on hemostasis by using ROTEM analysis. The results indicated that both propofol and sevoflurane have a negligible effect on hemostasis in the condition of minimal surgical trauma. In some previous studies that analyzed platelet function [2,3], propofol tended to inhibit platelet aggregation to a greater degree than sevoflurane. However, this study demonstrated that the hemostasis process in whole blood was ultimately comparable between the two groups.

Propofol and sevoflurane have been studied to reveal their effects on hemostasis. Propofol has shown inconsistent results in the previous studies. A research reported that propofol inhibited platelet aggregation in vivo and in vitro by increasing the intracellular calcium concentration [11]. In addition, it has been documented that propofol inhibited platelet aggregation induced by pro-inflammatory mediators such as lysophosphatic acid, platelet activating factor, and thromboxane A2 [12]. Hirakata et al. [13] proved that, low-concentration (7.1 μg/ml) propofol enhanced platelet aggregation in vitro, whereas high-concentration (17.8 μg/ml) propofol suppressed platelet aggregation. In this study, clinically administered propofol concentration is 3-4 μg/ml, which corresponds to the low concentration of propofol according to Hirakata et al. [13], and our results should have shown the acceleration of platelet aggregation. However, postoperative ROTEM values were not different from the

### Table 2. Preoperative Hematologic Laboratory Results

<table>
<thead>
<tr>
<th></th>
<th>TIVA (n = 33)</th>
<th>SEVO (n = 33)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Hb (g/dl)</td>
<td>12.7 ± 1.6</td>
<td>11.9 ± 1.9</td>
<td>0.056</td>
</tr>
<tr>
<td>Plt (×10\textsuperscript{3}/μl)</td>
<td>241 ± 96</td>
<td>280 ± 81</td>
<td>0.105</td>
</tr>
<tr>
<td>PT INR</td>
<td>1.1 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>0.510</td>
</tr>
<tr>
<td>aPTT (sec)</td>
<td>35.7 ± 2.7</td>
<td>35.4 ± 3.5</td>
<td>0.864</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>263 ± 93</td>
<td>307 ± 161</td>
<td>0.627</td>
</tr>
</tbody>
</table>

The values are presented as the mean ± SD. aPTT: activated partial thromboplastin time, Hb: hemoglobin, Plt: platelets count, PT-INR: international normalized ratio of prothrombin time.

### Table 3. Preoperative and Postoperative Values of ROTEM Measurements in Both Groups

<table>
<thead>
<tr>
<th>Reference values</th>
<th>Preoperative</th>
<th>Postoperative</th>
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<tbody>
<tr>
<td></td>
<td>TIVA (n = 33)</td>
<td>SEVO (n = 33)</td>
</tr>
<tr>
<td></td>
<td>TIVA (n = 33)</td>
<td>SEVO (n = 33)</td>
</tr>
<tr>
<td>INTEM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT (s)</td>
<td>100-240</td>
<td>160.4 ± 19.6</td>
</tr>
<tr>
<td>CFT (s)</td>
<td>30-110</td>
<td>74.7 ± 22.7</td>
</tr>
<tr>
<td>α (°)</td>
<td>70-83</td>
<td>75.4 ± 4.0</td>
</tr>
<tr>
<td>MCF (mm)</td>
<td>50-72</td>
<td>61.0 ± 6.2</td>
</tr>
<tr>
<td>EXTEM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT (s)</td>
<td>38-79</td>
<td>52.0 ± 7.1</td>
</tr>
<tr>
<td>CFT (s)</td>
<td>34-159</td>
<td>87.4 ± 29.9</td>
</tr>
<tr>
<td>α (°)</td>
<td>63-83</td>
<td>72.7 ± 5.5</td>
</tr>
<tr>
<td>MCF (mm)</td>
<td>50-72</td>
<td>58.2 ± 4.3</td>
</tr>
<tr>
<td>FIBTEM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCF (mm)</td>
<td>9-25</td>
<td>13.5 ± 4.1</td>
</tr>
</tbody>
</table>

The values are presented as the mean ± SD. α: alpha angle, CT: clotting time, CFT: clot formation time, MCF: maximum clot firmness.
preoperative ones, and postoperative $\text{MCE}_{\text{platelet}}$ was not significantly different from the preoperative one in the TIVA group. Similarly, in an in vitro study, propofol at clinical sedative or anesthetic concentration was proved to have no inhibitory effect on platelet aggregation [14].

Unlike propofol, sevoflurane has shown consistent results in impairing platelet function or inhibiting platelet aggregation [2,3,15,16]. Sevoflurane only inhibited platelet aggregation induced by weak agonist, through suppressing cyclooxygenase activity [2,16]. However, platelet aggregation induced by the strong agonist, thrombin, was not inhibited by sevoflurane. This is because thrombin is more powerful in inducing platelet aggregation and calcium release [2,17]. In the SEVO group of our study, preoperative ROTEM values were also comparable to the postoperative ones. Postoperative $\text{MCE}_{\text{platelet}}$, representing the platelet component of clot strength, was increased compared to the preoperative one in the SEVO group, even though it had no statistical significance. Platelet aggregation by thrombin cannot be excluded completely even in the less invasive and less traumatic ophthalmic surgery, and sevoflurane effect on hemostasis does not seem to overcome platelet aggregation by thrombin.

Platelet function was proved previously to be more impaired during propofol-anesthesia than isoflurane-or sevoflurane-anesthesia [3,4]. However, our results did not show any significant difference in postoperative ROTEM parameter as well as $\text{MCE}_{\text{platelet}}$ value. This suggests that whole blood hemostasis may not be influenced by anesthetic agents, even though platelet function itself can be impaired more by propofol than by sevoflurane. Or, we measured the ROTEM parameter at postoperative 1 h. Although the plasma concentration of propofol and sevoflurane were not evaluated, the anesthetic effect could disappear at postoperative 1 h. Thus, our postoperative ROTEM values might be comparable between the SEVO and TIVA groups. This can be verified by the intraoperative ROTEM analysis.

We recruited patients undergoing minimally-invasive optical surgeries to minimize the acceleration of coagulability by surgical trauma. Thus, we could not verify the implication of $\text{MCE}_{\text{platelet}}$ changes in other clinical situations. Further study focusing on surgical blood loss and surgical view with ROTEM analysis can ascertain the clinical implication of the
different anesthetic technique.

We recognize some limitations in this study. First, sevoflurane concentration was titrated independently of the BIS in the SEVO group. The end-tidal anesthetic concentration of inhalation anesthetics was reported to correlate poorly with the BIS [18]. Thus, intraoperative vital signs were the guide for sevoflurane titration during anesthetic maintenance in the SEVO group, and the intraoperative anesthetic depth was believed to be appropriate in the SEVO group. Second, this study was not blinded to the anesthetic care provider. However, the ROTEM analyses were automatically performed by a ROTEM® Coagulation Analyzer, and we believed that bias would be minimal, even though the anesthetic care provider was not blinded.

In conclusion, this study did not provide evidence that different anesthetic agents have different hemostatic effects. Propofol and sevoflurane showed a negligible effect on coagulation and platelet component of clot strength according to ROTEM analyses. However, analysis of ROTEM parameters during the anesthesia or at the end of the anesthesia remains to be investigated.

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REFERENCES