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Effects of Isoflurane, Sevoflurane, and Desflurane on Platelet Function: A Prospective, Randomized, Single-Blind, In Vivo Study

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ABSTRACT

Background: The primary physiologic function of platelets is to facilitate hemostasis by aggregation. Volatile anesthetics have been reported to decrease platelet aggregation in vivo and in vitro.

Objective: The aim of this study was to investigate the hematologic effects of the anesthetics isoflurane, sevoflurane, and desflurane on hemoglobin (Hb), hematocrit (Hct), platelet count, activated partial thromboplastin time (aPTT), prothrombin time (PT), international normalized ratio (INR), and platelet aggregation after minor surgery.

Methods: Patients aged 20 to 60 years who were scheduled to undergo minor surgery and American Society of Anesthesiologists physical status P1 or P2 (healthy or mild systemic disease) were randomized to 1 of 3 groups: 1 minimum alveolar concentration (MAC) of isoflurane, sevoflurane, or desflurane. None of the patients received premedication. Anesthesia was induced using IV thiopental 5 to 6 mg/kg, fentanyl 1 to 2 μg/kg, and vecuronium 0.1 mg/kg, and maintained with 1 MAC of isoflurane, sevoflurane, or desflurane in 66% nitrous oxide and 33% oxygen. Vecuronium 0.03 mg/kg was given when necessary for muscle relaxation. All patients were monitored throughout surgery; isotonic saline was given at a rate of 5 mL/kg · h. Hematologic studies were performed preoperatively, 15 minutes after intubation, and 1 hour after the end of surgery. Platelet aggregation tests were performed in a laboratory using a platelet function analyzer (PFA), collagen/epinephrine PFA test cartridges, collagen/adenosine diphosphate PFA test cartridges, and PFA trigger solution.

Results: This prospective, randomized, single-blind, in vivo study was conducted at Gevher Nesibe Teaching Hospital, Erciyes University, Kayseri, Turkey. Thirty patients (15 men, 15 women) were randomized to the 3 treatment groups (each, n = 10). Hb, Hct, platelet count, aPTT, PT, and INR were statistically

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similar between all 3 groups. The measured parameters were not significantly different between the isoflurane and desflurane groups at any time point. However, in the sevoflurane group, mean (SD) platelet aggregation was significantly delayed 15 minutes after intubation and 1 hour after surgery compared with the preoperative values (collagen/epinephrine, 81.70 [9.85] seconds vs 196.20 [27.84] seconds and 115.40 [25.80] seconds; both, $P < 0.05$).

Conclusions: In this study of the effects of isoflurane, sevoflurane, and desflurane in patients undergoing minor surgery, clinically relevant antithrombotic effects were observed 15 minutes after intubation with all 3 drugs, although the effects in patients receiving sevoflurane were significantly greater compared with those in patients receiving isoflurane and desflurane. The antithrombotic effects of isoflurane and desflurane were not continued at 1 hour after surgery; however, the inhibitory effects of sevoflurane on platelet function were continued at 1 hour after surgery but were significantly decreased from levels found at 15 minutes after intubation. (*Curr Ther Res Clin Exp.* 2005;66:375–384)

Key words: isoflurane, sevoflurane, desflurane, platelet function, coagulation.

INTRODUCTION

Volatile anesthetics might decrease platelet aggregability in vivo and in vitro.[1–21] Effects of halothane on platelet function were first found by Ueda,[3] who showed that halothane inhibited adenosine diphosphate (ADP)–induced platelet aggregation using aggregometry in canine blood. Based on a MEDLINE search (key terms: *halothane, isoflurane, sevoflurane, desflurane,* and *platelet function*; years: 1960–2004), numerous studies have shown the effects of halothane, isoflurane, and sevoflurane on platelet function.[1–27] However, we found only 3 studies[14–16] of the effects of desflurane on platelet function and bleeding time, and the results of these studies differed.

Because the effects of desflurane on platelet function are unclear, we assessed the hematologic effects of isoflurane, sevoflurane, and desflurane on hemoglobin (Hb), hematocrit (Hct), platelet count, activated partial thromboplastin time (aPTT), prothrombin time (PT), international normalized ratio (INR), and platelet aggregation after minor surgery.

PATIENTS AND METHODS

This prospective, randomized, single-blind, in vivo study was conducted at Gevher Nesibe Teaching Hospital, Erciyes University, Kayseri, Turkey. Patients aged 20 to 60 years who were scheduled to undergo a minor elective surgical procedure (eg, knee arthroscopy, hand surgery) and American Society of Anesthesiologists physical status P1 or P2 (healthy or mild systemic disease) were eligible for the study. All patients provided written informed consent to participate. Approval for the study protocol was obtained from the ethics committee at the university.

Patients were excluded from the study for the following reasons: use of warfarin, herbal supplements, or NSAIDs, including aspirin; presence of a severe systemic disease, hypertension, diabetes mellitus, renal failure, gastrointestinal symptoms, or bleeding diathesis; or a history of allergy or sensitivity or contraindications to anesthetics. Patients were also excluded if they were unconscious, pregnant, or breast-feeding.

Before surgery, patients were randomized, in a 1:1 ratio using a computer-generated list of random numbers, to 1 of 3 treatment groups: 1 minimum alveolar concentration (MAC) of isoflurane, sevoflurane, or desflurane. None of the patients were administered premedication. Anesthesia was induced with IV thiopental 5 to 6 mg/kg, fentanyl 1 to 2 μg/kg, and vecuronium 0.1 mg/kg, and was maintained with 1 MAC of isoflurane, sevoflurane, or desflurane in 66% nitrous oxide and 33% oxygen. Fifteen minutes after endotracheal intubation, when end-tidal concentrations reached 1 MAC, the surgical procedure was started. When necessary, vecuronium 0.03 mg/kg was administered to maintain muscle relaxation.

Ventilation was performed to preserve end-tidal carbon dioxide concentration on expiration ($ETCO_2$) of 30 to 35 mm Hg. Patients were monitored throughout surgery and administered isotonic saline at 5 mL/kg · h during surgery. None of the patients were given a colloid infusion or a blood transfusion.

During surgery, electrocardiography and noninvasive automatic measurement of heart rate and blood pressure (measured in the contralateral arm) were performed, $ETCO_2$ and body temperature (AS/3, Datex-Engstrom, Inc., Helsinki, Finland) were measured, and arterial oxyhemoglobin saturation was monitored using pulse oximetry.

One hour before surgery, an 18-G cannula was inserted into a peripheral vein to collect blood specimens; that cannula was not used for IV fluid therapy. The specimens were collected preoperatively, 15 minutes after intubation, and 1 hour after the end of surgery. Blood specimens were collected into vacuum tubes (Vacutainer, Beckton, Dickinson and Company, Franklin Lakes, New Jersey) containing EDTA for measurement of Hb, Hct, and platelet count; 1.8-mL blood specimens were collected into vacuum tubes containing 3.2% sodium citrate for determination of aPTT, PT, and INR; and 3.6-mL blood specimens were collected into vacuum tubes containing 3.2% sodium citrate for determination of platelet aggregation. To prevent blood coagulation, the tubes of specimens were turned upside down 4 or 5 times. The tubes were sent to the Hematology and Coagulation Laboratories, Kayseri, Turkey, within 2 hours of collection. The tests were performed by hematologists blinded to treatment assignment.

Platelet aggregation tests were performed in the laboratory using a platelet function analyzer (PFA-100, Dade Behring Inc., Marburg, Germany), collagen/epinephrine (Col/Epi) PFA test cartridges, collagen/ADP (Col/ADP) PFA test cartridges, and PFA trigger solution (Dade Behring Inc.). The cartridges were stored at 2°C to 8°C and dwelled at room temperature for 15 minutes before testing. The PFA-100 device was adjusted to take measurements at 37°C.

The 2 test cartridges, Col/Epi and Col/ADP, were placed in the cassette of PFA-100 simultaneously, and an 800-μL blood specimen was infused through the small opening in the test cartridges, using a pipette. Trigger solution containing 11 mL of isotonic saline was spread on the membrane to solubilize Col/Epi or Col/ADP, and blood levels were measured. Coagulated specimens were not to be used, and results found to have system errors were not to be included in the analysis.

Statistical Analysis

Statistical analyses were carried out using Statistica version 4.3 (Statsoft Inc., Tulsa, Oklahoma). Variables are expressed as mean (SD). Because the Kolmogorov-Smirnov test revealed a normal distribution of the data, we used analysis of variance (ANOVA). For prestudy power and sample size calculation, assuming $\alpha = 0.05$ and a power of 80%, ~8 patients would be required in each group to detect a 20% increase in the estimated mean baseline Col/Epi and Col/ADP values of 80 (15) seconds (PS Power and Sample Size Calculations version 2.1.30, Microsoft Corporation, Redmond, Washington). To compensate for nonevaluable patients, we planned to enroll 10 patients per group. One-way ANOVA and the post hoc Tukey HSD test, when appropriate, were used for intergroup analyses, and ANOVA for repeated measures was used for intragroup analyses. $P < 0.05$ was considered statistically significant.

RESULTS

The study comprised 30 patients (15 men, 15 women) (10 per treatment group). No significant differences in demographic and clinical characteristics, duration of surgery, or hemodynamic properties were found between the 3 groups (**Table I**).

The effects of isoflurane, sevoflurane, and desflurane on Hb, Hct, platelet count, aPTT, PT, INR, and collagen before and after minor surgery are shown in **Table II**. No significant differences in Hb, Hct, or platelet count were found between the groups. No significant between-group differences in aPTT, PT, or INR measured at all 3 time points or in preoperative Col/Epi and Col/ADP levels were found. However, Col/Epi and Col/ADP values 15 minutes after intubation and 1 hour after surgery were significantly higher in the sevoflurane group compared with those in the isoflurane and desflurane groups (all, $P < 0.05$). Intragroup analyses showed that Col/Epi and Col/ADP levels significantly increased 15 minutes after intubation in all 3 groups (all, $P < 0.05$), and increased 1 hour after surgery in the sevoflurane group ($P < 0.05$). Significantly higher levels were observed in both Col/Epi and Col/ADP only in the sevoflurane group 1 hour after surgery (both, $P < 0.05$). However, Col/Epi and Col/ADP levels obtained at 1 hour after surgery were significantly lower compared with those obtained at 15 minutes after intubation in all 3 groups (all, $P < 0.05$).

Two specimens were excluded from analysis in the isoflurane group because of coagulation, and none of the specimens were excluded from the sevoflurane or desflurane groups.

Table I. Baseline demographic and clinical characteristics and hemodynamic properties of study patients (N = 30).* Values are presented as mean (SD) unless otherwise specified.

Characteristic	Isoflurane (n = 10)	Sevoflurane (n = 10)	Desflurane (n = 10)
Age, y	41.50 (9.94)	37.90 (9.82)	37.20 (7.26)
Weight, kg	73.80 (11.12)	75.70 (10.59)	70.90 (8.81)
Sex, no.			
Female	5	5	5
Male	5	5	5
Duration of surgery, min	71.40 (13.45)	79.10 (15.61)	67.70 (11.49)
Thiopental, mg	428.70 (47.21)	440.20 (52.31)	425.30 (50.92)
Vecuronium, mg	9.40 (1.73)	10.10 (1.10)	9.00 (1.05)
SAP, mm Hg	138.60 (20.03)	135.00 (11.78)	129.50 (11.44)
DAP, mm Hg	82.10 (5.89)	80.70 (6.76)	78.70 (7.02)
HR, bpm	82.10 (8.22)	83.40 (6.50)	75.50 (8.27)
SpO_2, %	97.10 (1.19)	98.30 (1.49)	97.04 (0.94)

SAP = systolic arterial pressure; DAP = diastolic arterial pressure; HR = heart rate; SpO_2 = arterial oxyhemoglobin saturation as monitored using pulse oximetry.
*No significant intergroup differences were found.

DISCUSSION

Isoflurane, sevoflurane, and desflurane did not significantly affect Hb, Hct, platelet count, aPTT, PT, or INR. Based on Col/Epi and Col/ADP levels, significantly increased platelet aggregation was observed with all 3 treatments at 15 minutes after intubation compared with preoperative levels. Platelet aggregation was significantly greater with sevoflurane compared with isoflurane and desflurane 15 minutes after intubation and 1 hour after surgery. The effects of desflurane and isoflurane were not significantly different from baseline 1 hour after surgery. Desflurane and isoflurane had similar effects on Col/Epi and Col/ADP.

The literature search revealed only 3 studies of the effects of desflurane on platelet function and bleeding time.[14–16] Frohlich et al[14] and Mielke et al[15] found that 0.5 MAC of desflurane did not affect platelet function. Berlet et al[16] reported that desflurane had differential effects, by impairing platelet aggregation while not affecting α-degranulation, on various aspects of platelet activation that are similar to those of halothane in healthy blood donors.

Such conflicting findings of studies of the effects of inhalational anesthetics on platelet aggregation might be ascribed to the fact that measurement methods, induction agents, MACs, and test tubes were found to vary in both in vivo and in vitro studies.[3–21] The PFA-100 device best simulates injuries in the vessel

Table II. Effects of isoflurane (n = 8), sevoflurane (n = 10), and desflurane (n = 10) on hemoglobin (Hb), hematocrit (Hct), platelet count, activated partial thromboplastin time (aPTT), prothrombin time (PT), international normalized ratio (INR), and collagen before and after minor surgery. Values are presented as mean (SD).

Parameter/Study Drug	Before Surgery (Baseline)	15 Minutes After Intubation	1 Hour After Surgery
Hb, g/dL			
Isoflurane	13.99 (1.36)	13.24 (1.29)	13.58 (1.45)
Sevoflurane	13.96 (1.40)	12.85 (2.01)	13.61 (1.43)
Desflurane	13.72 (1.42)	13.27 (1.18)	13.66 (1.20)
Hct, %			
Isoflurane	41.41 (4.07)	39.05 (4.25)	40.42 (4.29)
Sevoflurane	41.99 (4.06)	38.74 (5.60)	40.89 (4.45)
Desflurane	49.47 (4.29)	39.38 (3.64)	40.40 (3.96)
Platelet count, cells × 10^3/μL			
Isoflurane	276.10 (35.08)	266.60 (42.82)	286.10 (42.21)
Sevoflurane	282.10 (552.92)	250.00 (44.09)	274.60 (53.80)
Desflurane	272.80 (396.14)	260.20 (37.57)	274.20 (33.94)
aPTT, s			
Isoflurane	32.85 (4.28)	34.15 (4.19)	31.41 (4.29)
Sevoflurane	35.08 (3.07)	37.56 (3.71)	34.01 (5.13)
Desflurane	31.20 (3.54)	33.21 (4.12)	31.34 (3.45)
PT, s			
Isoflurane	12.14 (0.73)	12.68 (0.85)	12.88 (0.77)
Sevoflurane	12.15 (0.91)	12.64 (1.02)	12.10 (0.86)
Desflurane	12.31 (0.84)	12.71 (0.97)	12.52 (0.79)
INR			
Isoflurane	1.02 (0.05)	1.05 (0.07)	1.07 (0.06)
Sevoflurane	1.01 (0.09)	1.07 (0.11)	1.03 (0.07)
Desflurane	1.04 (0.10)	1.06 (0.10)	1.03 (0.03)
Collagen/epinephrine, s			
Isoflurane	85.70 (9.11)	119.40 (19.11)	101.60 (13.73)*
Sevoflurane	81.70 (9.85)	196.20 (27.84)†‡	115.40 (25.80)*†‡
Desflurane	82.30 (7.57)	100.60 (6.16)†	94.50 (7.93)*
Collagen/ADP, s			
Isoflurane	81.20 (7.37)	99.5 (12.25)†	85.60 (6.43)*
Sevoflurane	76.90 (7.23)	202.80 (37.80)†‡	100.30 (15.97)*†‡
Desflurane	78.80 (7.37)	93.60 (5.12)†	88.30 (7.81)*

ADP = adenosine diphosphate.
*$P < 0.05$ versus 15 minutes after intubation.
†$P < 0.05$ versus baseline.
‡$P < 0.05$ between groups.

walls in in vitro conditions. Flow cytometry, agrometry, spectrophotometry, thromboelastography, and Sonoclot analyses have all been used in previous studies; however, it has been reported that these devices are not as sensitive as the PFA-100 device.[3–11,17–24]

The failure to demonstrate inhibitory effects on platelets has been mainly attributed to inhalational anesthetics being volatilized in the tubes while blood specimens are stored before aggregation tests are performed.[11] In an in vitro study, De La Cruz et al[25] reported that vacuum test tubes prevented volatilization of anesthetic agents. We used the PFA-100 device, the sensitivity of which has been reported to be 90% to 95%, to measure platelet aggregation.[26,27] We also used vacuum test tubes to prevent volatilization of anesthetics and to avoid their contact with room air.

Antiaggregation effects of inhalation anesthetics have been investigated in many in vitro studies.[3,4,6,8–10,21] We investigated the effects of ADP and collagen on platelet aggregation, and statistically significant differences from baseline were found with 1 MAC of isoflurane and desflurane on platelet aggregation 15 minutes after intubation. These effects were probably not clinically significant, and they had resolved at 1 hour after surgery. During surgery, platelet activation causes the release of vasoactive substances (eg, serotonin, thromboxane). Platelets become temporarily hypoaggregable during surgery; after surgery they become hyperaggregable.[5] Using agrometry, Lichtenfeld et al[5] assessed the effects of volatile agents on platelet aggregation and reported that not only anesthetics, but also major surgical stresses, influenced platelet function. For this reason, we collected blood specimens 15 minutes after intubation (ie, before surgery) to avoid the effects of surgical stimulation on platelet function.

Although some investigators have reported that sevoflurane in various MACs had inhibitory effects on platelet aggregation,[10–14,21,24,27,28] others found that sevoflurane did not have such effects.[11,15,27] It may be that the methods and MACs used varied between the studies. Dordoni et al[12] studied the in vivo and in vitro effects of thiopental, propofol, and sevoflurane on platelet function during thyroid surgery and found that the combination of thiopental, fentanyl, and sevoflurane significantly reduced collagen-induced aggregation by the end of induction, whereas ADP-induced aggregation and thromboxane generation were unaffected. The combination of propofol, fentanyl, and sevoflurane had no effect on platelets. They also found that thiopental inhibited platelets in vitro in a dose-dependent manner, whereas fentanyl or propofol did not. The present study used the same thiopental/fentanyl induction protocol in the isoflurane, sevoflurane, and desflurane groups. In contrast to Dordoni et al,[12] we found that sevoflurane had considerable effects on platelets. Our results agree with those of Horn et al,[13] who studied the in vitro effect of 0.5 MAC of sevoflurane on platelet antigen expression and function in healthy volunteers, using flow cytometry, thromboelastography, and PFA measurements. They found that sevoflurane inhibited agonist-induced glycoprotein IIb/IIIa activation and surface expression on platelets in whole blood with subanesthetic concentrations in

vitro. Hirakata et al[21] found that isoflurane (0.28–0.84 mmol/L) did not influence the aggregation induced by ADP and epinephrine, but that sevoflurane (0.13–0.91 mmol/L) and halothane (0.49–1.25 mmol/L) inhibited secondary platelet aggregation induced by ADP and epinephrine without affecting primary platelet aggregation. They explained that sevoflurane exerted this inhibitory effect via suppression of cyclooxygenase activity and thromboxane A_2 (TxA_2) formation and that sevoflurane showed its antiaggregation effect, which is reversible, without changing TxA_2 receptor binding affinity. The authors also claimed that sevoflurane had a stronger inhibitory effect on secondary aggregation compared with halothane.

Dogan et al[11] found that sevoflurane had a considerable inhibitory effect on platelet aggregation in patients who underwent minor elective surgery, and a residual effect was seen 1 hour after surgery. Similarly, we did not find a significant between-group difference in Hb, Hct, platelet count, PT, aPTT, INR, or sevoflurane-inhibited platelet aggregation, as reported in previous studies.[10,11,13–15,21] One MAC of isoflurane, sevoflurane, and desflurane inhibited ADP- and epinephrine-induced platelet aggregation 15 minutes after intubation, but this inhibitory effect was higher in patients administered sevoflurane and continued at 1 hour after surgery. Berlet et al[16] studied the in vitro effects of desflurane and halothane on platelet activation in healthy volunteer blood donors, using ADP and collagen to stimulate platelets. Using Born aggregometry and flow cytometry to measure platelet response, the authors reported that desflurane had differential effects on various aspects of platelet activation that were similar to those of halothane. These reports consistently support our findings.

Yokubol et al[10] reported that sevoflurane suppressed cyclooxygenase activity and thus decreased TxA_2 formation, which in turn increased bleeding time in patients undergoing minor elective surgery. They also noted that despite the increase in bleeding time and inhibition of platelet aggregation, the amount of blood lost was too small to require blood transfusion in any patient. We agree with Yokubol et al[10] that the inhibitory effect of sevoflurane does not cause clinically important blood loss and that this loss is not important in patients with homeostasis. On the other hand, the inhibitory effects may be useful in that they decrease the risk for thrombogenic complications.[5]

We suggest that anesthetists should be aware of the potential impairment of the coagulation profile by anesthetic agents in surgery that poses a risk for severe hemorrhage and in patients with blood diathesis and thrombosis disorders.

CONCLUSIONS

In this study of the effects of isoflurane, sevoflurane, and desflurane in patients undergoing minor surgery, clinically relevant antithrombotic effects were observed 15 minutes after intubation with all 3 drugs, although the effects in patients receiving sevoflurane were significantly greater compared with those in patients receiving isoflurane and desflurane. The antithrombotic effects of

isoflurane and desflurane were not continued at 1 hour after surgery; however, the inhibitory effects of sevoflurane on platelet function were continued at 1 hour after surgery but were significantly decreased from levels found at 15 minutes after intubation.

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