J Anesth (1999) 13:193–196

Journal of
Anesthesia

Anesthesia with sevoflurane, but not isoflurane, prolongs bleeding time in humans

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Abstract

Purpose. Halothane has been shown to suppress platelet aggregation in vitro and ex vivo and to prolong bleeding time. In a previous in vitro study, we demonstrated that sevoflurane had a stronger suppressive effect on platelet aggregation than halothane. The present study investigated whether clinical use of sevoflurane affects bleeding time in vivo.

Methods. Thirty-four patients undergoing minor elective surgery were randomly assigned to sevoflurane or isoflurane. Anesthesia was induced with intravenous thiopental and maintained with sevoflurane or isoflurane with nitrous oxide. Bleeding time was measured by the Duke method. An initial (control) measurement was obtained in the operating room before the induction of anesthesia, and a second was obtained 5–10 min after endotracheal intubation but before starting the operation, when the end-expiratory concentration of sevoflurane or isoflurane had been stabilized at 1–1.5 times the minimum alveolar concentration (MAC), and the mean arterial pressures were between 80% and 120% of the preanesthetic values.

Results. Bleeding time was increased from the preanesthetic value of 2.07 ± 0.82 min to 2.83 ± 0.93 min (n = 15) in the sevoflurane group ($P < 0.01$) but was not significantly altered in the isoflurane group.

Conclusion. Sevoflurane alters bleeding time in the clinical situation.

Key words: Anesthesia, Sevoflurane, Isoflurane, Blood, Platelet aggregation, Bleeding time

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This study was presented in part at the 11th World Congress of Anesthesia, Sydney, Australia, 1996.

Received for publication on May 28, 1998; accepted on June 8, 1999

Introduction

Several in vitro investigations have compared the antiaggregatory effects of volatile anesthetics [1–6]. In previous in vitro studies, we showed that halothane suppressed secondary platelet aggregation more strongly than enflurane and isoflurane [5], and that sevoflurane had an even stronger antiaggregatory effect than halothane [6].

The effect of clinical anesthesia on platelet aggregability and bleeding time has also been evaluated by several investigators [7–10]. Dalsgaard-Nielsen et al. [8] demonstrated that platelet aggregability was altered in blood obtained during halothane anesthesia, resulting in a 54% prolongation of bleeding time. Fyman et al. [7] compared the effects of halothane, enflurane, isoflurane, and fentanyl-nitrous oxide anesthesia on bleeding time and found a 33% prolongation by halothane, but not by other volatile anesthetics.

We previously showed an alteration of platelet aggregability in blood obtained during sevoflurane anesthesia [11], but the bleeding time was not estimated. The present study was conducted to test whether the antiaggregatory effect of sevoflurane results in prolongation of bleeding time during clinical anesthesia with this anesthetic.

Methods

After the approval of the institutional ethics committee had been obtained, 34 patients undergoing minor elective surgery were included in the study. Informed consent was obtained from all patients before they underwent any study procedure. The patients were randomly assigned to the sevoflurane and isoflurane groups. None of the patients had a history of any hematological disorder, and none had taken drugs known to affect platelet aggregation within the last 2

weeks. Preoperative measurements, including complete blood count, platelet count, prothrombin time, partial thromboplastin time, electrolyte concentrations, and arterial blood gas tensions, were within normal limits. The patients were premedicated with intramuscular ranitidine 50 mg. Anesthesia was induced with intravenous thiopental 3–5 mg·kg^{-1} and vecuronium 0.1–0.15 mg·kg^{-1}, and was maintained with the volatile anesthetic to be tested together with 66% nitrous oxide in oxygen. After endotracheal intubation, inspiratory and end-expiratory vapor gas concentrations were monitored (Datex Capnomac Ultima, Datex Instrumentarium, Helsinki, Finland). Inspiratory concentrations of the volatile anesthetics were adjusted to maintain the end-expiratory concentrations at between 1 and 1.5 times the minimum alveolar concentration (MAC) and mean arterial pressures at 80%–120% of the preanesthetic values. Lactated Ringer's solution was infused intravenously, and no other drug was administered during this period. Body temperature was maintained between 35° and 37°C. Patients who could not maintain mean arterial pressure within 80%–120% of their preanesthetic values during the test period were excluded from further studies.

In 30 patients, bleeding time was measured twice by the Duke method [12]. A small cut was made in the earlobe using a blood lancet (Type FL-1, Futaba, Tokyo, Japan), and blood was blotted onto absorbent paper every 30 s to measure bleeding time. Measurements of bleeding time were carried out in the operating room immediately before induction of anesthesia (preanesthetic control, T_0) and 5–10 min after endotracheal intubation when the end-expiratory sevoflurane or isoflurane concentration was between 1.0 and 1.5 MAC (2.1%–3.0% and 1.2%–1.8%, respectively) (T_1).

The drugs used were sevoflurane (Maruishi Pharmaceutical, Osaka, Japan) and isoflurane (Dainabot, Osaka, Japan). Data are expressed as means ± SD. The difference in bleeding time at T_0 and T_1 was analyzed by the Wilcoxon signed-rank test, and the other data were analyzed by the Mann-Whitney test or Fisher's exact probability test. Differences with $P < 0.05$ were considered significant.

Table 1. Demographic data for patients studied

Anesthetic	Age (yr)	M/F	Body weight (kg)	ASA 1/2
Sevoflurane	43.1 ± 10.5	3/12	55.7 ± 6.8	12/3
Isoflurane	45.1 ± 12.3	2/13	56.2 ± 8.4	12/4

There were no significant differences between groups in patients' characteristics.

Results

The demographic data for the patients are presented in Table 1. There were no significant differences between the two groups in age, body weight, sex, ASA physical status, blood pressure, or heart rate. In three patients in the isoflurane group and one in the sevoflurane group, the mean arterial pressure at T_1 was outside 80%–120% of the preanesthetic value. These patients were excluded from further studies. The doses of anesthetics administered at T_1, and blood pressure and heart rate at T_0 and T_1, are shown in Table 2.

There was no significant difference between the two groups in bleeding time at T_0. In the isoflurane group, the bleeding time at T_1 was not significantly different from that at T_0. In the sevoflurane group, the bleeding time increased from 2.07 ± 0.82 min at T_0 to 2.83 ± 0.93 min at T_1 ($n = 15$; $P < 0.01$) (Fig. 1).

Discussion

The results clearly show that anesthesia with sevoflurane at clinical concentrations alters bleeding time. We used the Duke method, the most commonly used method of measuring bleeding time in Japan. This method is believed to be reliable because of the simplicity and clarity of the result, and it does not depend on the hand of the examiner. The examiner in our study was a well-trained individual who was not responsible for the anesthetic management of each case, and he used only one kind of blood lancet

Table 2. Anesthetic doses administered and cardiovascular parameters during test periods

	Dose administered between T_0 and T_1 (mg/kg)		Concentration of volatile anesthetics	Blood pressure (mmHg)		Heart rate (beats/min)	
Anesthetic	Thiopental	Vecronium	(MAC)	T_1	T_0	T_0	T_1
Sevoflurane	3.79 ± 0.45	0.115 ± 0.018	1.32 ± 0.326	96.5 ± 13.5	85.7 ± 23.5	71.4 ± 9.87	75.0 ± 12.1
Isoflurane	3.74 ± 1.08	0.111 ± 0.013	1.27 ± 0.202	98.0 ± 13.5	89.6 ± 14.3	72.7 ± 9.27	82.5 ±13.3

T_1 and T_0 represent time when the first (preanesthesia) and second measurements were performed.
Data are shown as means ± SD.

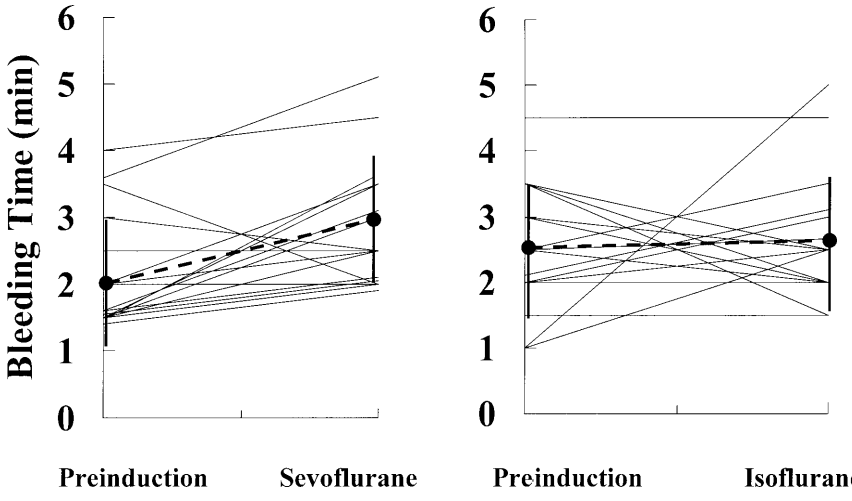

Fig. 1. Bleeding time before and after induction of anesthesia in each patient. *Dashed line* indicates the mean of 15 value 5

and absorbent paper throughout the experiment to minimize the deviation in results due to technical differences.

The measurements after the induction of anesthesia were carried out several minutes after endotracheal intubation but before starting the operation. It is therefore possible that endotracheal intubation induced stress responses, including increased catecholamine secretion, and that such responses may have affected the bleeding time. However, the fact that no alteration in bleeding time was induced by anesthetic induction with isoflurane argues against this.

Increased bleeding time can result from abnormal vascular integrity or a deficiency in von Willebrand factor, but it is more often caused by quantitative or qualitative platelet abnormalities. Suppression of platelet aggregability by volatile anesthetics, including halothane, methoxyflurane, diethyl ether, and cyclopropane, was first observed by Ueda in 1971. He ascribed this action of anesthetics to a nonspecific organic solvent effect [1]. A decade later, Walter et al. suggested that activation of platelet adenyl cyclase might contribute to the suppression of platelet aggregation by halothane [2]. Our previous in vitro study demonstrated that reduced binding affinity of thromboxane A_2 (TXA_2) receptors in platelets contributed to the antiaggregatory effect of halothane [5]. In contrast, the effect of sevoflurane may be ascribable to decreased TXA_2 formation, possibly by suppression of cyclooxygenase activity [6].

In spite of the suppression of platelet aggregability and prolongation of bleeding time by sevoflurane shown in the previous [6,11] and present studies, we are not aware of any reports in the literature suggesting increased blood loss or increased need for blood transfusion during general anesthesia with sevoflurane. This may be partly because the amount of hemorrhage during surgery depends more on surgical technique than on the bleeding tendency of an individual patient. Alternatively, we could speculate that the prolonged bleeding time induced by sevoflurane is not as prominent as the other effects of halothane and may not be clinically noticeable. However, in surgical and clinical conditions where even minor bleeding can have direct consequences [13–15], this effect of sevoflurane may need to be taken into account by clinical anesthesiologists.

We conclude that sevoflurane, but not isoflurane, prolongs bleeding time in the clinical situation. Further clinical studies are needed to elucidate the clinical significance of the present findings.

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