The Involvement of Adenosine Triphosphate-Sensitive Potassium Channels in the Different Effects of Sevoflurane and Propofol on Glucose Metabolism in Fed Rats

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BACKGROUND: Recently, we reported marked differences in the effects of sevoflurane and propofol on glucose metabolism; glucose use is impaired by sevoflurane, but not by propofol. Opening of adenosine triphosphate-sensitive potassium channels (K_{ATP} channels) in β islet cells attenuates insulin secretion, while inhibition of K_{ATP} channels in β islet cells increases insulin secretion. It is reported that volatile anesthetics open K_{ATP} channels, whereas propofol inhibits K_{ATP} channels. In this study, we examined the effects of sevoflurane and propofol on glucose metabolism under normovolemic and hypovolemic conditions, focusing on insulin secretion.

METHODS: Anesthesia was induced with sevoflurane (3% in 1 L/min oxygen) in all rats. After surgical preparation, rats were assigned to 2 groups. Anesthesia was maintained with sevoflurane (2% in 1 L/min oxygen) in the 1st group, and with propofol (a bolus dose of 30 mg/kg followed by continuous infusion at a rate of 30 mg · kg^{-1} · h^{-1}) in the 2nd group. Each group was divided into 3 subgroups: rats without pretreatment, rats pretreated with glibenclamide, and rats pretreated with nicorandil. After a 30-minute stabilization period, we withdrew 15 mL/kg of blood to induce hypovolemia. We evaluated glucose metabolism under both normovolemic and hypovolemic conditions by measuring blood glucose levels and plasma insulin levels.

RESULTS: Under both normovolemia and hypovolemia, glucose levels in rats anesthetized with sevoflurane were significantly higher than those in rats anesthetized with propofol, and insulin levels in rats anesthetized with sevoflurane were significantly lower than those in rats anesthetized with propofol. Glibenclamide, a K_{ATP} channel inhibitor, significantly decreased glucose levels and significantly increased insulin levels under sevoflurane anesthesia, suggesting that sevoflurane decreases insulin secretion by opening K_{ATP} channels in β islet cells. Glibenclamide significantly decreased glucose levels and significantly increased insulin levels under propofol anesthesia as well; however, insulin levels in rats pretreated with glibenclamide under propofol anesthesia were much higher than those in rats pretreated with glibenclamide under sevoflurane anesthesia. Furthermore, insulin levels in rats without pretreatment under propofol anesthesia seemed to be equal to or higher than those in rats pretreated with glibenclamide under sevoflurane anesthesia. These results suggest that there are marked differences in the effects of sevoflurane and propofol on insulin secretion regulated by K_{ATP} channels in β islet cells. Nicorandil, a K_{ATP} channel opener, produced no significant effects on glucose metabolism under both sevoflurane and propofol anesthesia.

CONCLUSIONS: Insulin secretion regulated by K_{ATP} channels in β islet cells is involved, at least in part, in the different effects of sevoflurane and propofol on glucose metabolism. (Anesth Analg 2012;114:110–6)

Control of blood glucose levels is an important concern in the anesthetic management of patients undergoing surgery, because intraoperative hyperglycemia is an independent risk factor for mortality and morbidity related to surgery.[1–3] Both glucose use and glucose production are modified by surgical stress; impaired insulin secretion results in decreased glucose use, while increased blood concentrations of catabolic hormones enhance glucose production.[4,5] Both sevoflurane, a volatile anesthetic, and propofol, an IV anesthetic, are popular drugs used for maintenance of general anesthesia in clinical settings. Recently, we reported that the effect of sevoflurane on glucose metabolism under aerobic conditions is markedly different from that of propofol in fed rats; glucose use is significantly impaired by sevoflurane, but not by propofol.[6] Several studies have reported that volatile anesthetics impair insulin secretion.[5,7–10] Volatile anesthetics open adenosine triphosphate-sensitive potassium channels (K_{ATP} channels),[11–13] whereas propofol inhibits K_{ATP} channels.[14–16] K_{ATP} channels in β islet cells play important roles in insulin secretion; opening of K_{ATP} channels in β islet cells attenuates insulin secretion, while inhibition of K_{ATP} channels in β islet cells increases insulin secretion.[17] Both

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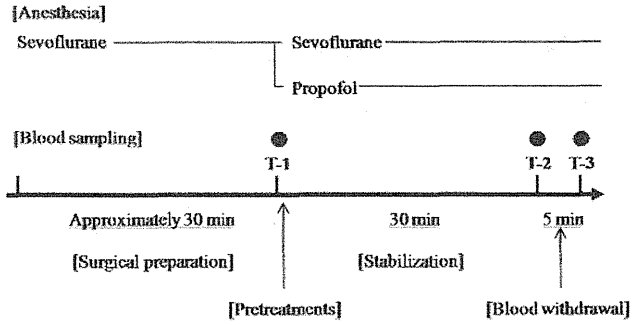

Figure 1. Experimental protocol. Surgical preparation was performed under sevoflurane anesthesia in all rats. After surgical preparation, anesthesia was maintained using either sevoflurane or propofol. Each group was divided into 3 subgroups: rats without pretreatment, rats pretreated with glibenclamide, and rats pretreated with nicorandil. We started blood withdrawal at 30 minutes after the surgical preparation. We sampled arterial blood at T-1 (i.e., immediately after surgical preparation), T-2 (i.e., just before blood withdrawal), and T-3 (i.e., immediately after completion of blood withdrawal).

anaerobic glucose metabolism as well as aerobic glucose metabolism can occur in patients undergoing surgery. Oxygen demand/supply imbalance induced by severe hemorrhage exaggerates anaerobic glucose metabolism. We thus examined the effects of sevoflurane and propofol on glucose metabolism under normovolemic as well as hypovolemic conditions in fed rats, focusing on insulin secretion regulated by K_{ATP} channels in β islet cells.

METHODS

Subjects

All experimental protocols were approved by the animal care committee of our institute. We used 9- to 10-week-old male Sprague–Dawley rats (Nippon Bio-Supply Center, Tokyo, Japan). Rats were housed in a regulated environment at an ambient temperature of 25°C under a 12-hour light–dark cycle (7 AM and 7 PM). Food (24% protein, 5% fat, 6% ash, 3% fiber, 8% water, and 54% nitrogen-free extract) and water were provided ad libitum until the experiments started. All experiments were performed between 9 AM and 5 PM. A heat lamp and a heating pad were used for the prevention of hypothermia during the experiments.

Experimental Protocols

The experimental protocols are summarized in Figure 1. We used 42 rats in this study. Anesthesia for surgical preparation was provided with sevoflurane (Maruishi Pharmaceutical Co., Ltd., Osaka, Japan). Sevoflurane (3% in 1 L/min oxygen) was administered via a tightly fitting mask for induction of anesthesia. All rats underwent tracheotomy and tracheal intubation. After tracheal intubation, sevoflurane (3% in 1 L/min oxygen) was administered via the tracheal tube, and the lungs were mechanically ventilated. Tidal volume was set at 2.5 mL, and respiratory rate was set at 60 breaths per minute. A 19-gauge catheter was inserted into the right carotid artery, and another 19-gauge catheter was inserted into the right jugular vein. All rats were administered 100 IU of heparin IV to maintain patency of the catheters. Immediately after surgical preparation, we recorded hemodynamic variables and sampled 1 mL of arterial blood (T-1).

Rats were assigned to 2 groups (group S and group P). We continued sevoflurane administration to rats in group S (n = 21); the inhaled concentration of sevoflurane was changed from 3% to 2%, and physiological saline (a bolus dose of 3 mL/kg followed by continuous infusion at a rate of 3 $mL \cdot kg^{-1} \cdot h^{-1}$) was administered IV. In rats in group P (n = 21), sevoflurane administration was discontinued, and instead propofol solution with a concentration of 10 mg/mL (AstraZeneca K. K., Osaka, Japan) was administered IV, with a bolus dose of 30 mg/kg followed by continuous infusion at a rate of 30 $mg \cdot kg^{-1} \cdot h^{-1}$. The doses of sevoflurane and propofol for maintenance of anesthesia were selected according to the protocol of our previous study.[6] At this time point, each group was divided into 3 subgroups (i.e., 7 rats per subgroup). Rats assigned to group S[-] and group P[-] received no pretreatment. Rats assigned to group S[g] and group P[g] were pretreated with 0.5 mg/kg of glibenclamide (Sigma–Aldrich Japan, Tokyo, Japan), a K_{ATP} channel inhibitor. Rats assigned to group S[n] and group P[n] were pretreated with 1 mg/kg of nicorandil (Chugai Pharmaceutical Co., Ltd., Tokyo, Japan), a K_{ATP} channel opener. Glibenclamide was dissolved in dimethyl sulfoxide (Sigma–Aldrich Japan) to a concentration of 1 mg/mL. Nicorandil was dissolved in physiological saline to a concentration of 2 mg/mL. Drugs for pretreatment were administered IV. To adjust total fluid load, we administered 0.5 mL/kg of physiological saline IV to rats in group S[-] and group P[-].

A 30-minute stabilization period was allowed, after which we recorded hemodynamic variables and sampled 1 mL of arterial blood (T-2). We then withdrew 15 mL/kg of blood via the arterial catheter at a rate of 3 $mL \cdot kg^{-1} \cdot min^{-1}$. Immediately after the blood withdrawal, we once again recorded hemodynamic variables and sampled 1 mL of arterial blood (T-3).

Measurements

The arterial catheter was connected to a low-volume pressure transducer for monitoring mean arterial blood pressure (MAP) and heart rate (HR). Immediately after each blood sampling, blood lactate levels and blood glucose levels were measured using a blood gas analyzer (i-STAT 1 Analyzer; Fuso Pharmaceutical Industries, Ltd., Osaka, Japan). Each blood sample was spun in a prerefrigerated centrifuge (4°C) at 1000 × g for 15 minutes, and plasma was stored at −60°C. Plasma insulin levels were measured by enzyme-linked immunosorbent assay using AKRIN-010T (Shibayagi Co., Ltd., Gunma, Japan).

Statistical Analysis

Data are shown as means ± SEM. Statistical analyses were performed using StatView version 5.0 (SAS Institute, Cary, NC) and JMP version 7.0.2. (SAS Institute). Homogeneity of variance was examined using Bartlett test. For comparisons of body weight and all experimental data at T-1 among all groups (i.e., 6 groups), we used 1-way analysis of variance (ANOVA); statistical significance was set at $P < 0.05$. For overall comparisons of serial data within each group, we used 1-way repeated-measures ANOVA; statistical significance was set at $P < 0.05$. For overall comparisons of serial data between 2 groups (i.e., between groups S[-] and P[-])

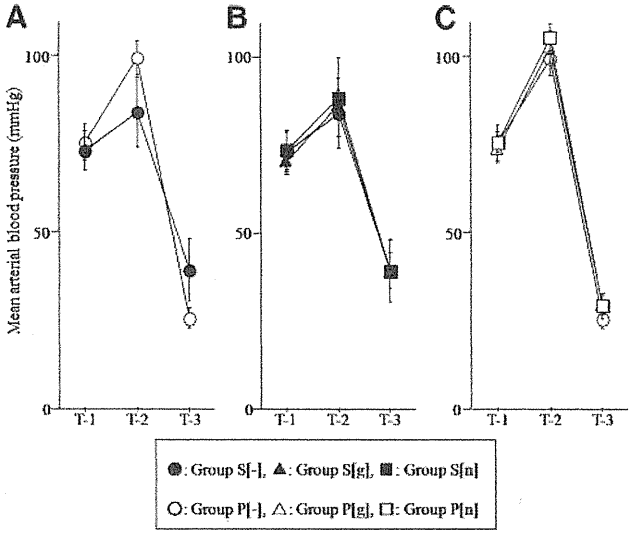

Figure 2. The time course of mean arterial blood pressure (MAP). A, Time course of MAP in groups S[-] and P[-]. There were no significant differences in the time courses between the 2 groups. B, Time course of MAP in groups S[-], S[g], and S[n]. There were no significant differences in the time courses among the 3 groups. C, Time course of MAP in groups P[-], P[g], and P[n]. There were no significant differences in the time courses among the 3 groups.

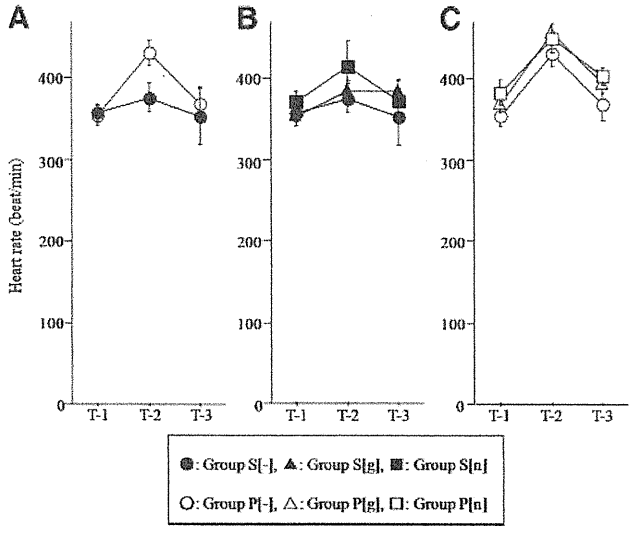

Figure 3. The time course of heart rate (HR). A, Time course of HR in groups S[-] and P[-]. There were no significant differences in the time courses between the 2 groups. B, Time course of HR in groups S[-], S[g], and S[n]. There were no significant differences in the time courses among the 3 groups. C, Time course of HR in groups P[-], P[g], and P[n]. There were no significant differences in the time courses among the 3 groups.

and among 3 groups (i.e., among groups S[-], S[g], and S[n] and among groups P[-], P[g], and P[n]), we used 2-way repeated-measures ANOVA, with group and time point as the factors; statistical significance was set at $P < 0.05$. We used Welch test for comparisons of blood lactate levels, blood glucose levels, and plasma insulin levels at each time point between the 2 groups; statistical significance was set at $P < 0.05$. We used 1-way ANOVA with Scheffé F test as a post hoc test for comparisons of blood glucose levels and plasma insulin levels at each time point among the 3 groups; statistical significance was set at adjusted $P < 0.05$.

RESULTS

Hemodynamics

There were no significant differences in body weight among the 6 groups. The time required for surgical preparation was approximately 30 minutes in all rats. All rats in the 6 groups survived throughout the experimental period.

There were no significant differences in MAP at T-1 among the 6 groups. Figure 2A shows the time course of MAP from T-1 to T-3 in groups S[-] and P[-]. Significant changes in MAP were observed in group S[-] ($P = 0.0027$, 1-way repeated-measures ANOVA). Significant changes in MAP were also observed in group P[-] ($P < 0.0001$, 1-way repeated-measures ANOVA). There were, however, no significant differences in the time course of MAP between groups S[-] and P[-]. As shown in Figure 2B, there were no significant differences in the time course of MAP among groups S[-], S[g], and S[n]. As shown in Figure 2C, there were no significant differences in the time course of MAP among groups P[-], P[g], and P[n].

There were no significant differences in HR at T-1 among the 6 groups. The time courses of HR from T-1 to T-3 in groups S[-] and P[-] are shown in Figure 3A. No significant changes in HR were observed in group S[-] over time. Significant changes in HR were observed in group P[-] ($P = 0.0022$, 1-way repeated-measures ANOVA). There were, however, no significant differences in the time course of HR between groups S[-] and P[-]. As shown in Figure 3B, there were no significant differences in the time course of HR among groups S[-], S[g], and S[n]. As shown in Figure 3C, there were no significant differences in the time course of HR among groups P[-], P[g], and P[n].

Blood Lactate Levels

There were no significant differences in lactate levels at T-1 among the 6 groups. The time course of lactate levels from T-1 to T-3 in groups S[-] and P[-] are shown in Figure 4A. Significant changes in lactate levels were observed in group S[-] ($P = 0.0002$, 1-way repeated-measures ANOVA). Significant changes in lactate levels were also observed in group P[-] ($P < 0.0001$, 1-way repeated-measures ANOVA). There were significant differences in the time course of lactate levels between groups S[-] and P[-] ($P = 0.0003$, 2-way repeated-measures ANOVA); lactate levels at T-3 in group P[-] were significantly higher than those in group S[-] ($P = 0.0158$, Welch test). As shown in Figure 4B, there were no significant differences in the time courses of lactate levels among groups S[-], S[g], and S[n]. As shown in Figure 4C, there were also no significant differences in the time course of lactate levels among groups P[-], P[g], and P[n].

Blood Glucose Levels

There were no significant differences in glucose levels at T-1 among the 6 groups. The time courses of glucose levels from T-1 to T-3 in groups S[-] and P[-] are shown in Figure 5A. No significant changes in glucose levels were observed in group S[-] over time. Significant changes in glucose levels were observed in group P[-] ($P < 0.0001$, 1-way

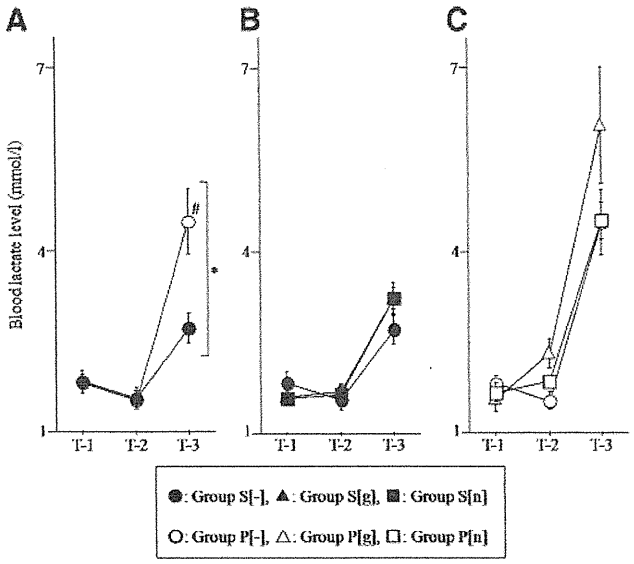

Figure 4. The time course of blood lactate levels. A, Time course of lactate levels in groups S[-] and P[-]. *There were significant differences in the time courses between the 2 groups, $P < 0.05$, 2-way repeated-measures analysis of variance. #$P < 0.05$ versus group S[-] at each time point, Welch test. B, Time course of lactate levels in groups S[-], S[g], and S[n]. There were no significant differences in the time courses among the 3 groups. C, Time course of lactate levels in groups P[-], P[g], and P[n]. There were no significant differences in the time courses among the 3 groups.

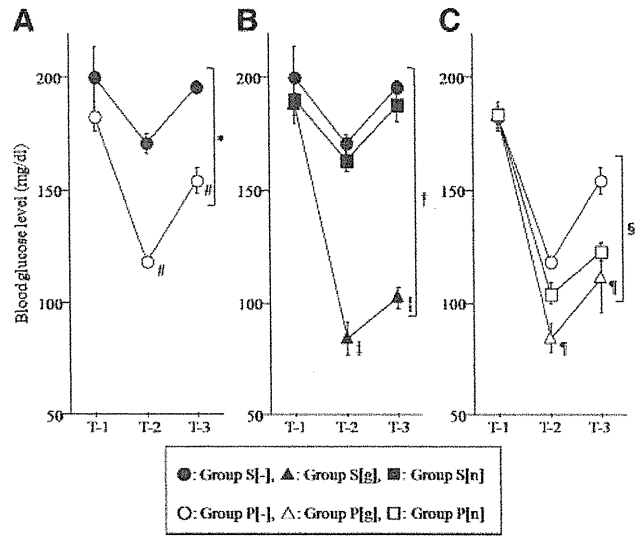

Figure 5. The time course of blood glucose levels. A, Time course of glucose levels in groups S[-] and P[-]. *There were significant differences in the time courses between the 2 groups, $P < 0.05$, 2-way repeated-measures analysis of variance (ANOVA). #$P < 0.05$ versus group S[-] at each time point, Welch test. B, Time course of glucose levels in groups S[-], S[g], and S[n]. †There were significant differences in the time courses among the 3 groups, $P < 0.05$, 2-way repeated-measures ANOVA. †Adjusted $P < 0.05$ versus group S[-] at each time point, Scheffé F test. C, Time course of glucose levels in groups P[-], P[g], and P[n]. §There were significant differences in the time courses among the 3 groups, $P < 0.05$, 2-way repeated-measures ANOVA. ¶Adjusted $P < 0.05$ versus group P[-] at each time point, Scheffé F test.

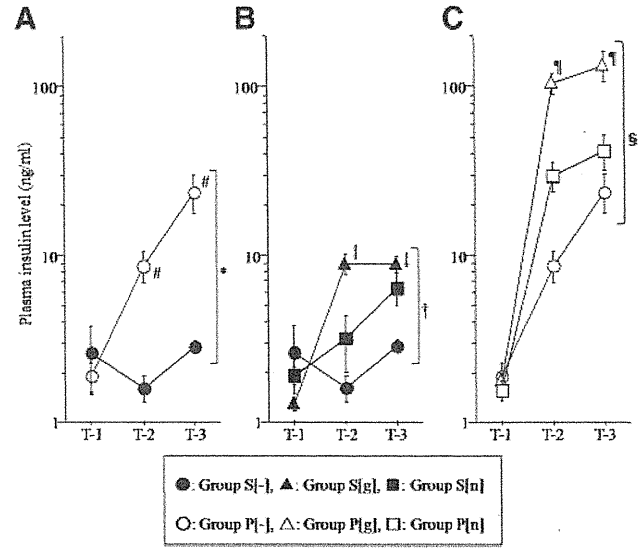

Figure 6. The time course of plasma insulin levels. The vertical axis is expressed in a logarithmic scale. A, Time course of insulin levels in groups S[-] and P[-]. *There were significant differences in the time courses between the 2 groups, $P < 0.05$, 2-way repeated-measures analysis of variance (ANOVA). #$P < 0.05$ versus group S[-] at each time point, Welch test. B, Time course of insulin levels in groups S[-], S[g], and S[n]. †There were significant differences in the time courses among the 3 groups, $P < 0.05$, 2-way repeated-measures ANOVA. †Adjusted $P < 0.05$ versus group S[-] at each time point, Scheffé F test. C, Time course of insulin levels in groups P[-], P[g], and P[n]. §There were significant differences in the time courses among the 3 groups, $P < 0.05$, 2-way repeated-measures ANOVA. ¶Adjusted $P < 0.05$ versus group P[-] at each time point, Scheffé F test.

repeated-measures ANOVA). There were significant differences in the time course of glucose levels between groups S[-] and P[-] ($P = 0.0402$, 2-way repeated-measures ANOVA); glucose levels at T-2 and T-3 in group P[-] were significantly lower than those in group S[-] ($P < 0.0001$ and $P = 0.0002$, respectively, Welch test). As shown in Figure 5B, there were significant differences in the time courses of glucose levels among groups S[-], S[g], and S[n] ($P < 0.0001$, 2-way repeated-measures ANOVA); glucose levels at T-2 and T-3 in group S[g] were significantly lower than those in group S[-] (adjusted $P < 0.0001$ and adjusted $P < 0.0001$, respectively, Scheffé F test). As shown in Figure 5C, there were significant differences in the time courses of glucose levels among groups P[-], P[g], and P[n] ($P = 0.0162$, 2-way repeated-measures ANOVA); glucose levels at T-2 and T-3 in group P[g] were significantly lower than those in group P[-] (adjusted $P = 0.0004$ and adjusted $P = 0.0225$, respectively, Scheffé F test).

Plasma Insulin Levels

There were no significant differences in insulin levels at T-1 among the 6 groups. The time course of insulin levels from T-1 to T-3 in groups S[-] and P[-] are shown in Figure 6A. No significant changes in insulin levels were observed in group S[-] over time. Significant changes in insulin levels were observed in group P[-] ($P = 0.0020$, 1-way repeated-measures ANOVA). There were significant differences in the time courses of insulin levels between groups S[-] and

P[-] ($P = 0.0007$, 2-way repeated-measures ANOVA); insulin levels at T-2 and T-3 in group P[-] were significantly higher than those in group S[-] ($P = 0.0087$ and $P = 0.0154$, respectively, Welch test). As shown in Figure 6B, there were significant differences in the time courses of insulin levels among groups S[-], S[g], and S[n] ($P < 0.0001$, 2-way repeated-measures ANOVA); insulin levels at T-2 and T-3 in group S[g] were significantly higher than those in group S[-] (adjusted $P = 0.0003$ and adjusted $P = 0.0021$, respectively, Scheffé F test). As shown in Figure 6C, there were significant differences in the time courses of insulin levels among groups P[-], P[g], and P[n] ($P < 0.0001$, 2-way repeated-measures ANOVA); insulin levels at T-2 and T-3 in group P[g] were significantly higher than those in group P[-] (adjusted $P < 0.0001$ and adjusted $P = 0.0011$, respectively, Scheffé F test).

DISCUSSION

Blood glucose levels at T-2 in group S[-] were significantly higher than those in group P[-], suggesting significant differences in the effects of sevoflurane and propofol on glucose metabolism under normovolemic conditions. Blood glucose levels at T-3 in group S[-] were significantly higher than those in group P[-], suggesting significant differences in the effects of sevoflurane and propofol on glucose metabolism under hypovolemic conditions.

Recently, we reported that glucose use under aerobic conditions in fed rats is significantly impaired by sevoflurane, but not by propofol.[6] Glucose use is affected by insulin secretion as well as by insulin sensitivity. K_{ATP} channels in β islet cells play important roles in insulin secretion; insulin secretion is decreased by opening K_{ATP} channels in β islet cells, but is increased by inhibiting K_{ATP} channels in β islet cells.[17] K_{ATP} channels consist of a pore-forming subunit (Kir6.1 or Kir6.2) and a regulatory subunit (sulfonylurea receptor; SUR1, SUR2A, or SUR2B); SUR1 coupled with Kir6.2 (SUR1/Kir6.2) forms K_{ATP} channels in β islet cells; SUR2A coupled with Kir6.2 (SUR2A/Kir6.2) forms K_{ATP} channels in cardiac myocytes; SUR2B coupled with Kir6.2 (SUR2B/Kir6.2) forms K_{ATP} channels in nonvascular smooth muscle cells; and SUR2B coupled with Kir6.1 (SUR2B/Kir6.1) forms K_{ATP} channels in vascular smooth muscle cells.[18–24] Glibenclamide, a K_{ATP} channel inhibitor, has a high affinity for SUR1, SUR2A, and SUR2B; however, nicorandil, a K_{ATP} channel opener, has a high affinity for SUR2A and SUR2B, but not for SUR1.[22–24]

Several studies reported that volatile anesthetics impair insulin secretion.[5,7–10] Volatile anesthetics open K_{ATP} channels,[11–13] and 1 study[25] reported that the opening effects of isoflurane on K_{ATP} channels in β islet cells contributed to attenuating insulin secretion, resulting in hyperglycemia. Plasma insulin levels at T-2 and T-3 in group S[-] were significantly lower than those in group P[-], implying that insulin secretion is involved, at least in part, in the different effects of sevoflurane and propofol on glucose metabolism under normovolemic as well as hypovolemic conditions. Glibenclamide significantly increased plasma insulin levels in rats under sevoflurane anesthesia, suggesting that sevoflurane decreases insulin secretion by opening K_{ATP} channels in β islet cells.

It was reported that propofol inhibited SUR1/Kir6.2, SUR2A/Kir6.2, and SUR2B/Kir6.2 expressed in COS-7 cells (African green monkey kidney cells), whereas propofol produced no significant effects on SUR2B/Kir6.1 expressed in COS-7 cells.[14] These results in in vitro studies suggest the possible inhibitory effects of propofol on K_{ATP} channels in β islet cells; however, the effects of propofol, at the doses used in clinical settings, on insulin secretion regulated by K_{ATP} channels in β islet cells have not been elucidated. In group P[-], plasma insulin levels at T-2 were significantly higher than those at T-1, suggesting that propofol ameliorated the immediately preceding inhibitory effects of sevoflurane on insulin secretion. Glibenclamide significantly increased plasma insulin levels in rats under propofol anesthesia in this study. Plasma insulin levels in group P[g] (104.4 ± 13.9 and 133.8 ± 27.6 ng/mL at T-2 and T-3, respectively) were much higher than those in group S[g] (8.8 ± 1.2 and 8.8 ± 1.0 ng/mL at T-2 and T-3, respectively). In addition, plasma insulin levels in group P[-] (8.7 ± 1.9 and 23.9 ± 6.3 ng/mL at T-2 and T-3, respectively) seemed to be equal to or higher than those in group S[g]. Taken together, these results suggest that there are marked differences in the effects of sevoflurane and propofol on insulin secretion regulated by K_{ATP} channels in β islet cells. We suppose that there are 2 possibilities. First, propofol increases insulin secretion by inhibiting K_{ATP} channels in β islet cells; however, propofol cannot completely inhibit them at the dose tested in this study. Second, propofol produces no significant effects on insulin secretion regulated by K_{ATP} channels in β islet cells.

Hemorrhage shock causes cardiac dysfunction. One study[26] reported that the inhibition of K_{ATP} channels in the cardiovascular system worsens hemorrhagic shock-induced myocardial ischemia, while the opening of K_{ATP} channels in the cardiovascular system prevents the extension of hemorrhagic shock-induced myocardial ischemia. Changes in cardiac function may induce significant alterations to metabolism. We thus compared hemodynamics and glucose metabolism under hypovolemic conditions among rats without pretreatment, rats pretreated with glibenclamide, and rats pretreated with nicorandil. There were no significant differences in hemodynamic variables at T-3 among groups S[-], S[g], and S[n] as well as among groups P[-], P[g], and P[n]. Nicorandil produced no significant effects on glucose metabolism at T-3 under sevoflurane anesthesia as well as propofol anesthesia. We therefore believe that the significantly increased insulin secretion at T-3 in groups S[g] and P[g] reflected the effects of glibenclamide on K_{ATP} channels in β islet cells under sevoflurane anesthesia and propofol anesthesia, respectively.

The decrease in oxygen delivery related to severe hemorrhage exaggerates peripheral oxygen demand/supply imbalance, leading to anaerobic glucose metabolism and increases in blood lactate levels.[27,28] Severe, uncompensated hemorrhage may attenuate the clearance rate of lactate, because blood perfusion to major organs, such as the liver, as well as peripheral tissues is decreased.[29] Therefore, both the increased production and the decreased clearance of lactate are responsible for the increased blood lactate levels during hemorrhagic shock. We believe that induction of anaerobic glucose metabolism contributed to

the significant increases in blood lactate levels under hypovolemic conditions in this study. Interestingly, blood lactate levels at T-3 in group P[-] were significantly higher than those in group S[-]. These results suggested that the increase in glucose use under hypovolemic conditions may lead to the enhancement of lactate production associated with anaerobic glucose metabolism, resulting in the significantly higher blood lactate levels.

We focused on insulin secretion to examine the different effects of sevoflurane and propofol on glucose metabolism in this study. Both insulin secretion and insulin sensitivity affect glucose use. Changes in both glucose use and glucose production are associated with stress-induced hyperglycemia. It is, therefore, necessary to examine the effects of the 2 anesthetics on insulin sensitivity and glucose production for further elucidation of their effects on glucose homeostasis. In this study, we used fed rats to avoid the possible effects of fasting on glucose metabolism; however, patients are usually made to fast before surgery in clinical settings. Thus, experiments using fasted animals are also required to elucidate the effects of the 2 anesthetics on glucose metabolism.

In conclusion, insulin secretion regulated by K_{ATP} channels in β islet cells is involved, at least in part, in the different effects of sevoflurane and propofol on glucose metabolism in fed rats.

DISCLOSURES

Name: Takayuki Kitamura, MD.
Contribution: Study design, conduct of study, data analysis, and manuscript preparation. Takayuki Kitamura attests to the integrity of the original data and the analysis.
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Contribution: Study design, conduct of study, data analysis, and manuscript preparation. Gaku Kawamura attests to the integrity of the original data and the analysis.
Name: Yoshitsugu Yamada, MD, PhD.
Contribution: Data analysis and manuscript preparation.
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ORIGINAL ARTICLE

Impact of remifentanil use on early postoperative outcomes following brain tumor resection or rectal cancer surgery

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Abstract
Purpose Remifentanil, a mu-opioid receptor agonist, has important characteristics for neuroanesthesia, but data about its effects on postoperative recovery and mortality are currently lacking.
Methods Using the Japanese Diagnosis Procedure Combination database in 2007, we selected patients who underwent elective brain tumor resection with open craniotomy under general anesthesia using either remifentanil or fentanyl and divided them into two categories: remifentanil patients and non-remifentanil patients. After propensity score matching for potential confounders, we compared the in-hospital mortality and postoperative length of stay (LOS) between the two groups. For comparison, the same endpoints were evaluated for patients underwent rectal cancer surgery under general anesthesia with intraoperative epidural anesthesia.
Results In patients who underwent brain tumor resection (936 pairs), remifentanil patients had significantly lower in-hospital mortality (1.5 % vs. 3.0 %; $P = 0.029$). Logistic regression analysis revealed that the odds ratio for use of remifentanil for in-hospital mortality was 0.47 (95 % confidence interval, 0.25–0.91; $P = 0.025$). Remifentanil patients also showed earlier discharge from hospital (median LOS, 17 vs. 19 days; hazard ratio, 1.19, 95 % confidence interval, 1.08–1.30; $P < 0.001$). In contrast, in 2,756 pairs of patients undergoing rectal cancer surgery, no significant difference was seen in either in-hospital morality (1.2 % vs. 1.3 %; $P = 0.518$) or median LOS (19 vs. 19 days; $P = 0.148$) between the two groups.
Conclusions Our data suggest a possible association between use of remifentanil and better early postoperative recovery for patients undergoing neurosurgery with craniotomy. Further studies, including a randomized controlled trial, are required to confirm the present results.

Keywords Remifentanil · Brain neoplasm · Neurosurgery · Postoperative outcome

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Introduction

Remifentanil, a mu-opioid receptor agonist, has a unique pharmacokinetic profile characterized by rapid equilibration with the central compartment and a short half-life that is independent of infusion duration [1, 2]. Although the use of remifentanil is common in Western countries [3], it was only approved in Japan in December 2006, and clinical use commenced in January 2007. We previously evaluated the population who received remifentanil during general anesthesia in 2007 using a nationwide administrative database in Japan and found that remifentanil was used in more than 40 % of all general anesthesia [4]. Patients with preoperative comorbidities including diabetes mellitus,

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hypertension, liver cirrhosis, and chronic renal failure were positively associated, whereas those with cardiac disease and co-application of epidural anesthesia were negatively associated, with the use of remifentanil [4]. The pharmacokinetics of remifentanil allows easy titration against changing intraoperative conditions as well as quick and predictable emergence from anesthesia without prolonged respiratory depression [5, 6]. These characteristics are especially important in neuroanesthesia because rapid postoperative recovery is essential for assessment of neurological function, making remifentanil a potentially ideal neuroanesthetic agent [7, 8]. Indeed, our recent evaluation revealed that populations with remifentanil were exceptionally high in neurosurgery [4]. However, reports about the effects of remifentanil beyond the operating theatre, i.e., its effects on postoperative recovery and mortality, have been lacking.

In the present study, we hypothesized that general anesthesia with remifentanil is associated with better postoperative recovery, especially for neurosurgery. To confirm this hypothesis, we conducted propensity score matching analyses to compare the postoperative outcomes between remifentanil patients and non-remifentanil patients for brain tumor resection, with a retrospective survey of a large administrative claims database in Japan. To determine whether the results from patients with brain tumor are also applicable to patients with other non-cephalocervical malignancies, we selected patients undergoing rectal cancer surgery with both epidural and general anesthesia and evaluated the same endpoints.

Materials and methods

Data source

The Diagnosis Procedure Combination (DPC) database is a patient classification system that is similar to the diagnosis-related groups used by Medicare in the United States. In 2002, the Ministry of Health, Labour and Welfare of Japan launched this case-mix system, and linked it with a lump-sum payment system. All 82 university teaching hospitals are obliged to adopt the DPC system; community hospitals can adopt it voluntarily. A survey of the DPC hospitals is conducted between July 1 and December 31 of each year by the DPC Research Group, funded by the Ministry of Health, Labour and Welfare [9–11]. Not only administrative claims data, but also detailed patient data, are collected for all inpatients discharged from the participating hospitals. In 2007, the number of participating hospitals was 926, and the number of patients included was 3 million, representing approximately 45 % of all inpatient admissions to acute care hospitals in Japan.

The database includes the following data: hospital locations; patients' age and sex; diagnoses, comorbidities at admission, and complications after admission recorded using text data in the Japanese language and the International Classification of Diseases, 10th Revision codes; procedures coded using Japanese original codes; anesthesia duration (min); dates when each drug was used; and lengths of stay (LOS) and discharge statuses. Information on the level of consciousness at admission is recorded for all patients and evaluated using the Japan Coma Scale (JCS). The JCS, which is based on the degree of arousal, is widely used by Japanese clinical facilities, including emergency services, for assessment of the consciousness level. The JCS and Glasgow Coma Scale assessments are well correlated [12].

This study was based on a secondary analysis of the administrative claims data. Given the anonymous nature of the data, the need for informed consent was waived. Study approval was obtained from the Institutional Review Board of the University of Occupational and Environmental Health (Kitakyushu, Fukuoka, Japan).

Patient selection

From the 3 million inpatients recorded between July 1 and December 31 in 2007, we selected patients who underwent elective brain tumor resection with open craniotomy under general anesthesia or rectal cancer surgery under general anesthesia accompanied with epidural anesthesia. In this study, we only included patients whose consciousness level at admission was "alert" (JCS = 0) and excluded patients with consciousness disorders (JCS $\geq$ 1) [12]. We also excluded patients with cerebrovascular diseases, chronic renal failure, or liver cirrhosis. We then selected patients who received fentanyl or remifentanil during general anesthesia and divided them into two subgroups: (a) patients who received both remifentanil and fentanyl, and (b) patients receiving fentanyl alone.

Patient background data

Patient background data that could potentially affect the study endpoints, including age, sex, and comorbidities, were assessed. The comorbidities assessed included hypertension, diabetes, chronic heart disease (ischemic heart disease, valvular heart disease, cardiomyopathy, or congenital heart disease), and chronic lung disease (emphysema, chronic bronchitis, bronchiectasis, asthma, interstitial lung disease, or pulmonary hypertension). We also verified the use of volatile anesthetic agents (sevoflurane, isoflurane, enflurane, or halothane) for each patient. We assessed the hospital inpatient volumes for brain tumor resection and rectal cancer surgery because

they could potentially affect the postoperative clinical outcomes, including mortality [9]. Hospital volumes were determined by the number of brain tumor resections or rectal cancer surgeries during the study period, using the unique identifier for each hospital.

Endpoints

The primary endpoint was in-hospital mortality. Postoperative LOS was assessed as a secondary endpoint.

Statistical analysis

We used propensity score matching [13] to adjust for differences in the baseline characteristics because the patients were not randomly assigned to receive remifentanil. We performed a one-to-one matched analysis on the basis of the estimated propensity scores for each patient. The log odds of the probability that a patient received remifentanil were modeled for potential confounders including age, sex, comorbidities (hypertension, diabetes mellitus, chronic lung diseases, or cardiovascular diseases), duration of anesthesia, and hospital volumes. C-statistics were calculated to evaluate the goodness of fit. The estimated logits were compared between the remifentanil patients and non-remifentanil patients, and a "match" occurred when one patient in the remifentanil group had an estimated logit within 0.6 SD of a patient in the non-remifentanil group. If two or more patients in the remifentanil group met this criterion, we randomly selected one patient for matching.

We compared the rates of in-hospital mortality between the remifentanil group and non-remifentanil group in brain tumor surgery and rectal cancer surgery using chi-square tests. For the logistic regression analyses, we performed univariate analyses between each covariate and in-hospital mortality in the first step. Then, age, sex, remifentanil use, and other covariates with a P value <0.10 were included in the final multivariate logistic regression models. The final models also adjusted for clustering of patients within hospitals using generalized estimating equations.

We compared the discharge rates of patients between the subgroups in each covariate using the Kaplan–Meier method and log-rank tests. Cox regression analyses were performed to model the concurrent effects of various factors on discharge, where we included age, sex, remifentanil use, and other covariates with a P value <0.10 in the log-rank tests.

We presented odds ratios (OR) and 95 % confidence intervals (95 % CI) for the logistic regressions and hazard ratios (HR) and 95 % CI for the Cox regressions. For the categorical variables, the OR (or HR) for the reference subgroup was 1.00, and the OR (or HR) for each of the other subgroups was presented in comparison with the reference subgroup. The threshold for significance was a P value <0.05. All statistical analyses were conducted using IBM SPSS version 19.0 (Statistical Package for Social Sciences, Chicago, IL, USA).

Results

Of the 3 million inpatients, we identified a total of 3,550 brain tumor resections and 11,142 rectal cancer surgeries between July and December of 2007. After inclusion of patients who were administered remifentanil or fentanyl and exclusion of those with consciousness disorders, cerebrovascular diseases, chronic renal failure, or liver cirrhosis, we selected 2,830 patients who underwent brain tumor resection under general anesthesia (1,891 with both remifentanil and fentanyl and 939 with fentanyl alone) and 8,205 patients who underwent rectal cancer surgery with general and epidural anesthesia (2,778 with both remifentanil and fentanyl and 5,427 with fentanyl alone). Using one-to-one propensity score matching, we selected 936 pairs of the remifentanil group and non-remifentanil group for brain tumor resection and 2,756 pairs for rectal cancer surgery. The C-statistics were calculated to be 0.592 and 0.541 for brain tumor resection and rectal cancer surgery, respectively.

Table 1 shows the patient background data of the 1,872 selected cases from the brain tumor resection and 5,512 from the rectal cancer surgery (including 4,610 low anterior resection and 902 abdominal perineal resection), divided into remifentanil group and non-remifentanil group. There were no significant differences in the patient background data between the two groups in each surgery.

Table 1 also shows the differences in the use of volatile agents between the two groups after propensity score matching. Overall, 1,351 patients received sevoflurane and 162 received isoflurane during brain tumor resection, whereas 4,344 received sevoflurane and 108 isoflurane during rectal cancer surgery. No patients received enflurane or halothane. The percentage of remifentanil patients receiving volatile agents was significantly lower than that of non-remifentanil patients in both the brain tumor resection group (68.9 % vs. 90.0 %; $P < 0.001$) and the rectal surgery group (73.9 % vs. 87.1 %; $P < 0.001$).

With regard to in-hospital mortality, a chi-square test revealed a significant difference between the remifentanil group and non-remifentanil group (1.5 % vs. 3.0 %; $P = 0.029$) in brain tumor resection but not in rectal cancer surgery (1.2 % vs. 1.3 %; $P = 0.630$). Table 2 shows results of logistic regression analyses for in-hospital mortality following brain tumor resection. In the multivariate model, the remifentanil group showed a significantly lower mortality than the fentanyl-alone group (odds ratio, 0.47,

Table 1 Patient background and use of volatile agents

	Brain tumor resection			Rectal cancer surgery		
	Fentanyl alone (n = 936)	Fentanyl and remifentanil (n = 936)	P	Fentanyl alone (n = 2,756)	Fentanyl and remifentanil (n = 2,756)	P
Patient background						
Age (mean ± SD)	55.2 ± 18.1	55.2 ± 17.0	0.876	65.1 ± 12.6	64.9 ± 13.5	0.645
Sex (male) (n, %)	427 (45.6 %)	427 (45.6 %)	1.000	1,741 (63.2 %)	1,755 (63.7 %)	0.695
Comorbidities (n, %)						
Hypertension	118 (12.6 %)	107 (11.4 %)	0.434	329 (11.9 %)	361 (13.1 %)	0.193
Diabetes	66 (7.1 %)	71 (7.6 %)	0.657	273 (9.9 %)	295 (10.7 %)	0.330
Cardiovascular diseases	39 (4.2 %)	33 (3.5 %)	0.471	254 (9.2 %)	258 (9.4 %)	0.853
Chronic lung diseases	7 (0.7 %)	8 (0.9 %)	0.795	71 (2.6 %)	80 (2.9 %)	0.458
Duration of anesthesia (min, mean ± SD)	434 ± 193	436 ± 181	0.853	323 ± 123	321 ± 122	0.624
Hospital volume for colorectal surgery (per 6 months; mean ± SD)	19.3 ± 15.7	18.3 ± 15.3	0.164	40.0 ± 39.8	39.8 ± 39.1	0.840
Use of volatile agents						
Nitrous oxide	230 (24.6 %)	57 (6.1 %)	<0.001	351 (12.7 %)	142 (5.2 %)	<0.001
Sevoflurane	751 (80.2 %)	600 (64.1 %)	<0.001	2,341 (84.9 %)	2,003 (72.7 %)	<0.001
Isoflurane	109 (11.6 %)	53 (5.7 %)	<0.001	64 (2.3 %)	44 (1.6 %)	0.052
Either or both: sevoflurane/isoflurane	842 (90.0 %)	645 (68.9 %)	<0.001	2,401 (87.1 %)	2,038 (73.9 %)	<0.001
Propofol	702 (75.0 %)	826 (88.2 %)	<0.001	2,158 (78.3 %)	2,462 (89.3 %)	<0.001

95 % CI, 0.25–0.91; $P = 0.025$). Older age was significantly associated with higher in-hospital mortality. Duration of anesthesia was not a significant predictor of in-hospital mortality. Other anesthetic agents including nitrous oxide, isoflurane, sevoflurane, or propofol were not significantly associated with in-hospital mortality.

The chi-square test showed no significant difference in in-hospital mortality following colorectal cancer surgery between the remifentanil group and non-remifentanil group (1.2 % vs. 1.3 %; $P = 0.518$). Table 3 shows results of logistic regression analyses for in-hospital mortality following rectal cancer surgery. Again, older age was a significant predictor of higher hospital mortality. Higher hospital volume was significantly associated with lower mortality. Remifentanil use was not associated with mortality.

Table 4 shows the results of log-rank tests for each covariate and the Cox proportional hazard regression analysis for discharge from hospital following brain tumor surgery. The median (95 % CI) values for LOS were 17 (16.2–17.8) days for the remifentanil group and 19 (17.8–20.2) days for the non-remifentanil group, and a log-rank test revealed a significant difference between the two groups ($P < 0.001$). In the log-rank tests, diabetes, cardiac diseases, hospital volume, nitrous oxide, isoflurane, and propofol showed $P > 0.10$, and therefore were not included in the Cox regression. In the Cox regression model, the remifentanil group showed significantly earlier discharge from hospital (hazard ratio, 1.19, 95 % CI, 1.08–1.30; $P < 0.001$) compared with the non-remifentanil group. Consequently, the postoperative LOS was significantly shorter for the remifentanil group than for the non-remifentanil group. Use of sevoflurane was not significantly associated with LOS. Male sex, older age, and longer duration of anesthesia were significantly associated with longer LOS.

Table 5 shows the results of log-rank tests for each covariate and the Cox regression analysis for rectal cancer surgery. No significant difference of median LOS was shown between the remifentanil group and non-remifentanil group (19 vs. 19 days; $P = 0.148$) No significant difference in discharge rates was seen between the remifentanil group and non-remifentanil group (hazard ratio, 1.04, 95 % CI, 0.99–1.10; $P = 0.141$).

Discussion

In this study, propensity score matching analyses revealed that patients who underwent brain tumor resection under general anesthesia with remifentanil showed reduced postoperative LOS and lower in-hospital mortality compared with non-remifentanil patients. In contrast, patients who underwent rectal surgery did not show any difference in postoperative LOS and in-hospital mortality.

Table 2 Logistic regression analyses for in-hospital mortality following brain tumor resection

	Univariate analysis			Multivariate analysis		
	OR	95 % CI	*P*	OR	95 % CI	*P*
Age (years)						
≤59	1.00			1.00		
60–74	1.40	0.53–3.65	0.497	1.21	0.45–3.25	0.698
≥75	5.70	2.29–14.2	<0.001	4.80	1.65–14.0	0.004
Sex						
Male	1.00			1.00		
Female	0.56	0.30–1.05	0.071	0.57	0.30–1.05	0.073
Diabetes	1.34	0.47–3.82	0.580			
Hypertension	1.48	0.65–3.37	0.352			
Cardiac diseases	2.73	0.95–7.86	0.063	1.77	0.66–4.71	0.253
Duration of anesthesia (h)	0.88	0.77–0.98	0.023	0.90	0.80–1.01	0.063
Hospital volume (per 6 months)						
Low (≤9)	1.00					
Medium (10–23)	0.75	0.37–1.53	0.433			
High (≥24)	0.51	0.23–1.14	0.102			
Remifentanil	0.49	0.26–0.94	0.032	0.47	0.25–0.91	0.025
Nitrous oxide	1.11	0.49–2.52	0.808			
Isoflurane	1.44	0.56–3.72	0.451			
Sevoflurane	1.95	0.86–4.43	0.109			
Propofol	1.34	0.57–3.25	0.490			

OR odds ratio, *CI* confidence interval

As expected, older age was a significant contributor to higher in-hospital mortality and longer postoperative LOS. Several preoperative and intraoperative factors were also associated with the outcomes. After adjustment for these variables, our data indicated that use of remifentanil was an independent factor for earlier discharge from hospital. Therefore, based on these data, use of remifentanil may lead to better early postoperative recovery in patients undergoing neurosurgery with craniotomy.

Limitations

Because the present data were based on the administrative claim database, several limitations of this study should be acknowledged and, therefore, we should interpret these results carefully. Most importantly, it was based on a nonrandomized retrospective study. Although we used propensity score matching to adjust for differences in the baseline characteristics, the results could have been biased by several unmeasured confounders. For instance, no data were available regarding tumor size or anatomical location. Although we included patients undergoing elective neurosurgery whose preoperative consciousness was alert (JCS = 0) and adjusted for duration of anesthesia because of its presumed association with the level of surgical procedure difficulty, the tumor size or anatomical location should be a direct indicator of the difficulty or invasiveness of the neurosurgical procedures, which may affect postoperative recovery.

We should also be aware of intangible factors such as the clinician's choice for rather newly introduced drugs. Anesthesiologists in Japan may be prudent in choosing remifentanil and apply it for those patients with fewer comorbidities, although that seems unlikely in neurosurgery, because they chose remifentanil for more than 60 % of the patients [4]. After adjusting patients' backgrounds by propensity score matching, use of remifentanil favorably affected postoperative outcome in neurosurgery but not in rectal cancer surgery. These results suggest that the experience or preference of the anesthesia care provider was not linked to remifentanil use and a better postoperative outcome. Nevertheless, we cannot completely neglect these possible effects.

Second, we could not evaluate the doses of anesthetics and concurrent effects of various other drugs that could potentially have affected postoperative outcomes. Although we performed regression analyses for other anesthetics and found no other agent significantly contributed to early postoperative outcomes, further studies, including a randomized controlled trial, are required to confirm the present results and to explore the underlying mechanism behind the better postoperative recoveries observed in the remifentanil group.

Third, postoperative LOS is much longer in Japan compared with other advanced nations. Nearly 80 % of

Table 3 Logistic regression analyses for in-hospital mortality following rectal cancer surgery

	Univariate analysis			Multivariate analysis		
	OR	95 % CI	*P*	OR	95 % CI	*P*
Age (years)						
≤59	1.00			1.00		
60–74	2.14	0.96–4.81	0.064	1.89	0.88–4.09	0.104
≥75	6.18	2.88–13.3	<0.001	5.43	2.54–11.6	<0.001
Sex						
Male	1.00			1.00		
Female	0.79	0.48–1.32	0.369	0.76	0.44–1.31	0.318
Diabetes	1.12	0.54–2.36	0.756			
Hypertension	0.77	0.35–1.70	0.523			
Cardiac diseases	1.26	0.60–2.65	0.536			
Chronic lung diseases	3.42	1.46–8.04	0.005	2.46	1.06–5.67	0.035
Procedure						
Low anterior resection	1.00			1.00		
Abdominoperineal resection	1.65	0.95–2.87	0.074	1.64	0.92–2.93	0.094
Hospital volume (per 6 months)						
Low volume (≤20)	1.00		0.007	1.00		
Medium volume (21–39)	0.61	0.35–1.04	0.071	0.67	0.37–1.20	0.176
High volume (≥40)	0.38	0.20–0.71	0.003	0.46	0.24–0.86	0.016
Remifentanil	1.06	0.84–1.34	0.631	1.09	0.68–1.75	0.727
Nitrous oxide	0.76	0.36–1.59	0.465			
Isoflurane	2.28	0.70–7.35	0.169			
Sevoflurane	1.30	0.70–2.44	0.406			
Propofol	0.77	0.43–1.39	0.384			

OR odds ratio, *CI* confidence interval

patients undergoing intracranial parenchymal tumor resection are discharged within 7 days postoperatively in the United States [14]. Generally, the average postoperative LOS is much longer in Japan than in most medical centers in the United States, reflecting differences in the expectations of patients and, more so, in the healthcare delivery systems (i.e., the predominantly managed care in the United States versus a highly centralized, government-funded healthcare program in Japan) [15]. Even with the different healthcare delivery systems, the present results showed that older age contributed negatively to earlier discharge, which coincides with other reports from Western countries [16, 17].

Fourth, we cannot predict the long-term outcomes of patients using this database. Opioids are generally recognized as suppressors of natural killer cell activities and potentially contribute to tumor metastasis [18]. Although remifentanil is quickly eliminated from the bloodstream, we should also be careful for the long-term outcomes of patients receiving high-dose opioids during surgery.

Speculations for the mechanisms

We can speculate on several possible mechanisms for the current results.

General anesthesia with remifentanil may provide more suitable conditions for neurosurgery compared with general anesthesia with other drugs. Remifentanil patients were anticipated to be exposed to a lesser amount of volatile anesthetics than non-remifentanil patients. Opioids, including remifentanil and fentanyl, do not have any effects on intracranial pressure and carbon dioxide reactivity [19–21], whereas volatile anesthetics contribute to brain swelling because of their vasodilatory effect [22–24]. Remifentanil-based anesthesia may suppress intraoperative increases in blood glucose [25, 26] that could damage intact and/or ischemic neurons. Remifentanil is known to strongly suppress surgical stress responses, sustaining the early postoperative period in comparison to fentanil-based or sevoflurane anesthesia [25, 27–29].

In contrast, the use of remifentanil did not cause any significant difference in postoperative outcomes for rectal cancer surgeries that were conducted under general anesthesia with intraoperative epidural anesthesia. This neuraxial blockade is used for blocking afferent noxious stimuli from surgical sites to the central nervous system and reduces the total amount of volatile anesthetics used. Epidural anesthesia also attenuates the surgical stress response and reduces postoperative morbidity [30] after major abdominal surgery [31], coronary artery bypass grafting

Table 4 Log-rank tests and Cox regression analysis for discharge from hospital following brain tumor resection

	Log-rank tests			Cox regression[a]		
	Median LOS	95 % CI	*P*	Hazard ratio	95 % CI	*P*
Age (years)						
≤49	17	15.9–18.1	<0.001	1.00		
50–69	18	17.2–18.8		0.90	0.81–1.00	0.049
≥70	21	18.8–23.2		0.70	0.61–0.80	<0.001
Sex						
Male	19	17.7–20.3	<0.001	1.00		
Female	17	16.3–17.7		1.25	1.14–1.37	<0.001
Diabetes						
No	18	17.3–18.7	0.450			
Yes	18	15.2–20.8				
Hypertension						
No	17	16.3–17.7	0.013	1.00		
Yes	22	19.1–24.9		0.89	0.77–1.03	0.131
Cardiac diseases						
No	18	17.3–18.7	0.784			
Yes	19	15.4–22.6				
Chronic lung diseases						
No	18	17.4–18.6	0.099	1.00		
Yes	29	15.1–42.9		0.67	0.40–1.12	0.130
Hospital volume (per 6 months)						
Low (≤9)	18	16.8–19.2	0.607			
Medium (10–23)	18	17.0–19.0				
High (≥24)	17	15.8–18.2				
Duration of anesthesia (min)						
≤240	15	14.1–15.9	0.002	1.00		
241–360	16	15.1–16.9		0.93	0.79–1.09	0.389
≥361	19	18.0–20.0		0.76	0.66–0.89	<0.001
Remifentanil						
Non-users	19	17.8–20.2	<0.001	1.00		
Users	17	16.2–17.8		1.19	1.08–1.30	<0.001
Nitrous oxide						
Non-users	18	17.3–18.7	0.666			
Users	18	16.5–19.5				
Isoflurane						
Non-users	18	17.3–18.7	0.595			
Users	18	16.0–20.0				
Sevoflurane						
Non-users	17	16.1–17.9	0.012	1.00		
Users	18	17.1–18.9		0.91	0.82–1.02	0.095
Propofol						
Non-users	17	15.3–18.7	0.169			
Users	18	17.3–18.7				

LOS length of stay, *CI* confidence interval

[a] Before evaluating hazard ratio for a specific confounding factor, effects of all other factors are excluded

[32], and labor/delivery [33]. Subclinical increases in blood glucose are also attenuated with epidural anesthesia [34]. For patients who underwent rectal surgery, we believe that adequate suppression of the stress response may have been achieved with epidural anesthesia, and as a consequence, the use of supplemental remifentanil would not have added any further benefit.

Both volatile anesthetics and opioids have neuroprotective properties for ischemia [35–37]. Remifentanil is known to have *N*-methyl-D-aspartate receptor (NMDAR)

Table 5 Log-rank tests and Cox regression analysis for discharge from hospital following rectal cancer surgery

	Log-rank tests			Cox regression[a]		
	Median LOS	95 % CI	*P*	Hazard ratio	95 % CI	*P*
Age (years)						
≤49	18	17.4–18.6	<0.001	1.00		
50–69	19	18.4–19.6		0.97	0.92–1.04	0.408
≥70	21	20.2–21.8		0.87	0.81–0.93	<0.001
Sex						
Male	20	19.5–20.5	<0.001	1.00		
Female	18	17.5–18.5		1.11	1.05–1.17	<0.001
Diabetes						
No	19	18.6–19.4	0.022	1.00		
Yes	19	17.7–20.3		0.94	0.86–1.03	0.186
Hypertension						
No	19	18.6–19.4	0.127			
Yes	18	17.2–18.8				
Cardiac diseases						
No	19	18.6–19.4	0.550			
Yes	19	17.6–20.4				
Chronic lung diseases						
No	19	18.6–19.4	0.151			
Yes	20	18.3–21.7				
Procedure						
Low anterior resection	17	16.6–17.4	<0.001	1.00		
Abdominoperineal resection	28	26.7–29.3		0.60	0.56–0.64	<0.001
Hospital volume (per 6 months)						
Low (≤20)	22	21.3–22.7	<0.001	1.00		
Medium (21–39)	18	17.4–18.6		1.18	1.10–1.26	<0.001
High (≥40)	17	16.4–17.6		1.40	1.31–1.49	<0.001
Remifentanil						
Non-users	19	18.4–19.6	0.148	1.00		
Users	19	18.5–19.5		1.04	0.99–1.10	0.141
Nitrous oxide						
Non-users	18	17.2–18.8	0.225			
Users	19	18.5–19.5				
Isoflurane						
Non-users	19	18.6–19.4	0.557			
Users	19	16.8–21.2				
Sevoflurane						
Non-users	18	17.3–18.7	0.167			
Users	19	18.5–19.5				
Propofol						
Non-users	19	18.1–19.9	0.125			
Users	19	18.6–19.4				

LOS length of stay, *CI* confidence interval

[a] Before evaluating hazard ratio for specific confounding factor, effects of all other factors are excluded

agonist activity [38] and is associated with opioid-induced hyperalgesia [39]. NMDAR agonists are known to enhance neuronal activity and have been considered to contribute to ischemic neuronal damage [40]. On the other hand, NMDAR antagonists also exerted detrimental effects in patients who had a stroke [41]. Recently, a small dose of NMDA was reported to have preconditioning effect [42]. Based on these publications, optimal NMDA receptor activity is crucial for neuroprotection. General anesthesia with remifentanil, usually combined with other NMDA

antagonists such as sevoflurane and propofol, may possibly (coincidentally) provide an optimal NMDA signaling balance for neuroprotection.

Based on these lines of evidence, general anesthesia with remifentanil may provide optimal surgical conditions, reduce ischemic tissue damage, and attenuate postoperative as well as intraoperative stress responses, resulting in better early postoperative conditions for neurosurgical patients, although we should be aware of methodological limitations related to a retrospective survey.

In conclusion, the present data indicate a possible association between remifentanil use and earlier postoperative recovery in patients undergoing neurosurgery, and this finding warrants further prospective investigations.

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NEUROSCIENCES AND NEUROANAESTHESIA

Bispectral index is related to the spread of spinal sensory block in patients with combined spinal and general anaesthesia

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Editor's key points

- Previous publications described a relationship between the depth of sedation as measured by the bispectral index (BIS) and spinal sensory block height in patients with light to no additional sedation.
- In this study, BIS significantly correlates with the spread of spinal sensory block under conditions of identical predicted effect-site concentration of propofol.

Background. A relationship between the depth of sedation as measured by the bispectral index (BIS) and spinal sensory block height in patients with light to no additional sedation has been described previously. The present study was designed to investigate the hypothesis that BIS values closely correlate with the spread of spinal sensory block in patients deeply sedated with an i.v. target-controlled infusion of propofol.

Methods. Subjects comprised 100 patients aged 20–64 yr and undergoing arthroscopic knee surgery. Patients were given spinal anaesthesia with bupivacaine 0.5% (3 ml). Propofol was administered to achieve a target effect-site concentration of 3.0 μg ml^{-1}. The relationship between the spinal sensory level at 15 min after spinal anaesthesia and BIS values during 1–5, 6–10, 11–15, and 16–20 min time intervals after the estimated effect-site concentration reached 3.0 μg ml^{-1} was evaluated.

Results. The sensory level of spinal analgesia significantly and strongly correlated with BIS values during each time period after the estimated effect-site concentration remained at 3.0 μg ml^{-1} ($P<0.0001$). The correlation coefficient values were 0.8 during 1–5 min, 0.844 during 6–10 min, 0.801 during 11–15 min, and 0.804 during 16–20 min time periods.

Conclusions. We demonstrated that BIS values significantly correlate with the level of spinal sensory block under deep sedation with propofol. The depth of sedation induced by spinal anaesthesia depends on the spread of spinal sensory block.

Keywords: anaesthesia, depth; anaesthetic techniques, subarachnoid; anaesthetics i.v., propofol; monitoring, bispectral index

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Spinal anaesthesia has been noted to exert sedative effects.[1–4] Clinically, patients given high spinal anaesthesia frequently exhibit a decrease in alertness, with drowsiness becoming more frequent and pronounced as the spread of spinal block becomes higher. It has also been reported that the extent of spinal anaesthesia influences the depth of sedation, measured by the bispectral index (BIS) and previously reported to be in the range of 65–75.[5 6] However, BIS is sensitive to internal or external circumstances surrounding the patient and can be affected by abrupt arousal, movement, coughing, or noise in patients with light or no additional sedation.[7–9] There have not been enough data fully quantifying the relationship between BIS and the spread of spinal block during effect compartmental controlled propofol sedation. The present study aimed at investigating the hypothesis that BIS values closely correlate with the spread of spinal anaesthesia when patients are under deep sedation.

Methods

The study was approved by the Ethics Committee of Nihon University School of Medicine (Ref: 06/0903) and written informed consent was obtained from all patients. Subjects comprised 100 patients aged 20–64 yr [mean age, 37.8 (10.9) yr] with ASA physical status I and with a BMI between 18.5 and 30 who were undergoing elective arthroscopic knee surgery without tourniquets under spinal anaesthesia combined with general anaesthesia with a duration of <60 min. Exclusion criteria included any history of substance abuse, known allergic disorders, current prescriptions, psychological, cardiovascular, or neurological diseases, regular consumption of alcohol, cigarettes, or both, the use

of any psychoactive medicines such as benzodiazepines, antidepressants, anticonvulsants, antihistamines, opiates, or recreational drugs during the 10 yr before the day of surgery, and the use of any medicines for common cold including antihistamines during the 3 months before the day of surgery that would be expected to affect the EEG response. The interspaces through which the spinal anaesthetic was administered (L2–3, L3–4, or L4–5) were randomly selected using sealed envelopes. Patients were also randomly allocated by selection of sealed envelopes to tilting the bed upwards, horizontal, or downwards during and for 1 min after receiving spinal anaesthesia. The angle at which the bed was tilted was left to the discretion of the attending anaesthetist to provide an adequate spinal level for the surgery. The aim of the randomization was to produce various levels of spinal anaesthesia.

No patients received any premedications. I.V. access was established in a forearm vein before arrival at the operating theatre. The operating theatre was warmed to prevent an increase in EMG activity due to shivering. Standard monitoring devices (Bedside Station, BSS-9800, Nihon Kohden Corporation, Tokyo, Japan) including ECG, non-invasive arterial pressure measurement (NIAP), and arterial oxygen saturation via pulse oximetry (Sp_{O_2}) were applied and baseline values of vital signs were obtained. All patients received an i.v. colloid solution before initiation of the spinal anaesthesia at a rate of 20 ml kg^{-1} h^{-1} and at a rate of 30 ml kg^{-1} h^{-1} after spinal injection of the local anaesthetics until completion of data collection to prevent cardiovascular depression. Thereafter, additional hydration was done by administration of a Ringer's lactate solution according to the discretion of the attending anaesthesiologists. Heart rate, NIAP, and Sp_{O_2} were continuously monitored and recorded every 2.5 min using an electronic anaesthesia chart. Before spinal anaesthesia, the BIS electrodes were placed in the fronto-temporal regions as recommended by the manufacturer (Aspect Medical Systems, Norwood, MA, USA) and connected to an EEG monitor (*A-2000 ver. 2.1*, Aspect Medical Systems) for BIS measurement. Smoothening rate was set at 15 s. To reduce skin/electrode impedance, the skin over the forehead was cleaned with an alcohol-impregnated skin wipe. The attending anaesthesiologists could view BIS and SQI values throughout the study. The BIS values were only considered valid when SQI was above 50%. If SQI was below 50% for 1 min, BIS values for that minute were excluded from data analysis. If SQI was $<50\%$ for longer than 20% of the total study period, all data for the patient were excluded from analysis. All data were retrieved from the monitors after completion of each anaesthesia and stored for later analysis.

All anaesthetic procedures were conducted by a board-certified anaesthetist. Once BIS readings were stable, the patient was positioned in the lateral decubitus position with his/her surgical leg dependent. Bed tilting (upwards, horizontal, or downwards) was performed before subarachnoid puncture. Subarachnoid puncture was performed with a 25 G Sprotte needle (Spinocan, B. Braun Melsungen AG, Melsungen, Germany) at the L2–3, L3–4, or L4–5 space. After injection of intradermal local anaesthesia with mepivacaine 1% (2 ml) at the puncture site, plain hyperbaric bupivacaine 0.5% (3 ml) (Marcaine 0.5%, AstraZeneca, Osaka, Japan) (15 mg) was administered into the subarachnoid space. Cerebrospinal fluid aspiration (0.1 ml) was done to confirm correct needle placement before and after spinal drug administration. The bed tilting was maintained until 1 min after administration of the anaesthetic agent, whereafter the patient was turned to the supine position. Sensory block height was evaluated bilaterally using a pinprick test with the sharp tip of a safety pin every 1 min until 15 min after the initiation of the spinal anaesthesia. Bilateral sensory block level was segmentally confirmed to remain at the same level with three consecutive evaluations at 15 min after the administration. Complete motor block of the lower limbs was also confirmed at 15 min after subarachnoid drug administration. If the patients were able to flex either knees or ankles or the sensory block did not extend rostral to the operative site, spinal anaesthesia was readministered and the patient was excluded. Arterial pressure was measured every minute after spinal administration. Hypotension and bradycardia were defined as systolic arterial pressure below 80 mm Hg and heart rate below 45 beats min^{-1}, respectively, according to the definition by Reich and colleagues.[10] If hypotension or bradycardia persisted for more than 1 min, ephedrine or atropine, respectively, was administered i.v. and the patient was excluded from the study since these drugs affect the central nervous system. In addition, all patients had previously been informed that the spread of spinal anaesthesia could reach thoracic or cervical levels due to the bed tilting. If patients complained of any symptoms due to spinal anaesthesia, for example, nausea or dyspnoea, they were scheduled to be immediately sedated and excluded from the study. After checking the adequacy of spinal anaesthesia, a urinary catheter and rectal thermometer was inserted. The rectal temperature was maintained at 36.0–37.0°C using a forced-air warming blanket.

Patients were sedated with i.v. administration of propofol after confirmation of the level of the sensory block. All patients received plasma target-controlled infusion using the Diprifusor syringe pump (TERUMO Inc., Tokyo, Japan).

General anaesthesia was induced with i.v. propofol and vecuronium after preoxygenation. The target plasma concentration of propofol was initially set at 6.0 $\mu g\ ml^{-1}$. After loss of consciousness and confirmation of the absence of a difficult airway, vecuronium bromide was administered i.v. at a dose of 1 mg kg^{-1} to facilitate the insertion of a laryngeal mask airway (LMA) and controlled ventilation of the lungs. No further doses of vecuronium were administered. The LMA was inserted 2.5 min after the administration of propofol, and the plasma target concentration of propofol was subsequently reduced to 3.0 $\mu g\ ml^{-1}$. If LMA insertion could not be successfully completed at the first attempt, the target concentration of propofol was maintained at 6.0 $\mu g\ ml^{-1}$ until successful insertion was achieved and the patient was excluded. The patient's lungs were ventilated

with an oxygen and air (1:2) mixture, maintaining normocapnia and Sp_{O_2} above 98% using a respiratory frequency of 10 bpm and an inspiration to expiration ratio of 1:1.5. BIS values over the 20 min period after propofol plasma effect-site concentration equilibration at 3.0 μg ml^{-1} were recorded for further analysis.

If the BIS value was above 65 for more than 30 s or above 60 for more than 3 min, the attending anaesthesiologists could increase or add anaesthetics and the patient was excluded from analysis.[11 12] The patients remained unstimulated during data collection; surgery commenced after completion of data collection. All patients who participated in this study were interviewed on postoperative day 1 to inquire about intraoperative awareness.

Data analysis

Data analysis was performed by a blinded investigator. The maximum height of the sensory block on both sides was averaged and expressed as the spinal thoracic level. The spinal thoracic level of anaesthesia is expressed from 0.0 to 12.0, in which 0.0, 1.0, and 2.0 correspond to C8, Th1, and Th2, respectively. BIS values at 20 min after the effect-site concentration of propofol reached and remained at 3.0 μg ml^{-1} were divided into 1–5, 6–10, 11–15, and 16–20 min periods and mean BIS values were calculated separately for each of these periods. Correlation was evaluated between spinal thoracic levels at 15 min after spinal anaesthesia and the corresponding BIS values at the same time. Correlation was also evaluated between spinal thoracic levels at 15 min after spinal anaesthesia and the averaged BIS values for the periods 1–5, 6–10, 11–15, and 16–20 min after the effect-site concentration equilibration at 3.0 μg ml^{-1}. Statistical analysis was performed by Spearman's rank correlation coefficient by rank test to evaluate the correlation between the spinal thoracic level and the BIS value. Data were expressed as mean (standard deviation).

Results

Six of the 100 patients were excluded. Four were excluded because of the use of ephedrine or atropine to treat hypotension or bradycardia (two patients each). One patient was excluded from analysis because of unsuccessful LMA insertion at the first attempt. One patient was excluded because of poor SQI. The remaining 94 patients (male/female, 59/35) completed the study without missing data nor adverse events. The height and weight were 166.3 (8.7) cm and 66.3 (11.3) kg, respectively [BMI, 23.9 (3.2)].

Spinal anaesthesia was successfully performed in all the patients. Both sufficient spinal sensory block for surgery and complete motor block of the lower limbs were obtained in all the patients. No patients complained of severe or moderate symptoms due to the spinal anaesthesia. The consumption of propofol adjusted to body weight from the start of induction till the time when the effect-site concentration reached 3.0 μg ml^{-1} was approximately equal among patients. The consumption of propofol was 3.47 (0.02), 4.14 (0.02), 4.78 (0.02), 5.39 (0.02), and 5.99 (0.02) mg kg^{-1}, respectively, at 0, 5, 10, 15, and 20 min after the effect-site concentration reached 3.0 μg ml^{-1}. The mean time interval from the time when the target effect-site concentration was reduced and set at 3.0 μg ml^{-1} to the time when the concentration reached 3.0 μg ml^{-1} was 11 min and 15 s. No patients reported awareness during general anaesthesia at the postoperative interviews on the day of surgery or on postoperative day 1.

Data from one representative patient are presented in Figure 1 as an example. The mean BIS values for this patient were 37.6 during 1–5 min, 39.0 during 6–10 min, 40.0 during 11–15 min, and 36.8 during 16–20 min time interval after the effect-site concentration of propofol reached and remained at 3.0 μg ml^{-1}.

Mean baseline BIS values on admission to the operating theatre were 97.4 (0.5). Mean BIS values at 15 min after spinal bupivacaine administration were 97.1 (0.8). The spinal thoracic level did not significantly correlate with the BIS value at 15 min after spinal anaesthesia (Fig. 2). The correlation coefficient for this time was 0.135 (P=0.195). Spinal

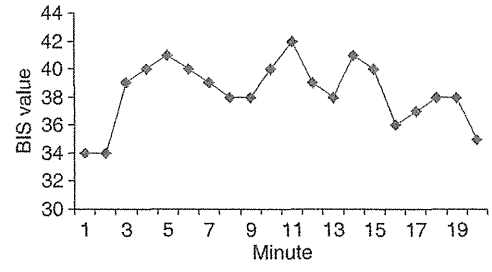

Fig 1 BIS values of one representative patient during 1–20 min after the effect-site concentration of propofol reached and remained 3.0 μg ml^{-1}.

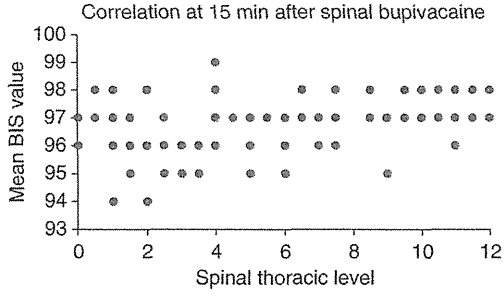

Fig 2 Scattergram showing the relationship between the spinal thoracic level of spinal sensory blockade and BIS values at 15 min after the spinal administration of bupivacaine. The correlation coefficient for this time was 0.135 (P=0.195). Spinal anaesthesia itself did not cause any significant decreases in BIS values at 15 min after spinal anaesthesia.