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Original Article

The Effects of Changing from Isoflurane to Desflurane on the Recovery Profile during the Latter Part of Anesthesia

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It is not known whether changing from isoflurane to desflurane during the latter part of anesthesia shows early emergence and recovery in long surgery. We therefore evaluated the effects of changing isoflurane to desflurane on emergence and recovery. Eighty-two patients were randomly assigned to receive isoflurane (Group I) or desflurane (Group D) or to change from isoflurane to desflurane anesthesia (Group X). At the point when there was an hour until the operation would end, isoflurane was replaced with 1 MAC of desflurane in Group X, and isoflurane and desflurane were maintained at 1 MAC in Groups I and D. When the operation ended, we compared the emergence and recovery characteristics among the 3 groups. Compared with Group I, Group X showed faster emergence and recovery. Group X and Group D showed similar emergence and recovery. In conclusion, changing isoflurane to desflurane during the latter part of anesthesia improves emergence and recovery.

Key words: desflurane, isoflurane, laparotomy, recovery

Recovery from anesthesia is influenced by the choice of anesthetic agent. The new inhaled anesthetics have markedly improved the quality and the time required for recovery compared with older anesthetics. Desflurane, in particular, is a new inhaled anesthetic agent with a very low blood-gas partition coefficient, which allows for rapid emergence and recovery at the end of surgery [1-4]. However, desflurane is more expensive to administer than other inhalational anesthetics [5].

Isoflurane is a commonly used inhaled volatile anesthetic agent because it is relatively inexpensive

despite its high solubility [6]. Attempts to combine the advantages of rapid emergence from desflurane with the lower cost of the more soluble isoflurane have proved to be ineffective [7, 8]. However, these studies were carried out with a small sample size and outside of clinical situations including volunteers and rats. In addition, the duration of anesthesia and the cross-over time were short. In addition, the authors have previously reported that changing from enflurane to desflurane during the latter part of anesthesia improves emergence and recovery in a long operation [9].

We hypothesized that in clinical situations having a longer duration of anesthesia and cross-over time, changing from isoflurane to desflurane anesthesia improves emergence and recovery. We therefore designed a double-blind prospective randomized study

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This trial is registered with ANZCTR (ACTRN12610000013066).

to test the hypothesis that when anesthetized patients undergo a laparotomy lasting 3 or more hours, changing from isoflurane to desflurane result in earlier emergence and recovery than pure isoflurane anesthesia and nearly equal emergence and recovery characteristics with pure desflurane anesthesia.

Materials and Methods

The study was approved by the Institutional Review Board at the Chung-Ang University College of Medicine and was registered with ANZCTR (ACTRN1261000013066). This study was carried out according to the principles of the Declaration of Helsinki, 2000, and written informed consent was obtained from all the participants.

Patients and groups. All patients undergoing laparotomy expected to last for 3 or more hours under general anesthesia at Chung-Ang University Hospital, Department of Surgery, who were between 18 and 65 years of age were candidate for inclusion in this study. The operations included in this study were total gastrectomy, subtotal gastrectomy, liver lobectomy, liver segmentectomy, colectomy, hemicolectomy, and Whipple's operation. Patients with clinically significant pulmonary, cardiovascular, hepatic, renal, hematologic, neurologic, or metabolic diseases and those who were chronic users of drugs that are known to affect anesthetic requirements were excluded from the study.

The patients were randomly assigned, using Excel random number generation, into 3 groups: an isoflurane group (Group I), a desflurane group (Group D), or a changing from isoflurane to desflurane group (Group X). Allocation concealment was achieved by placing the randomization sequence for each subject in sequentially numbered sealed brown envelopes. After admission to the operating room, and just before induction of anesthesia, the appropriate numbered envelope was opened and the card inside told if the patient was to be in Group I, Group D, or Group X.

General anesthesia. All patients were transferred to the operating room without premedication. Anesthesia was induced with 4–5 mg/kg thiopental, 0.1 mg/kg vecuronium, and 2 μ g/kg fentanyl. Standard monitoring (including electrocardiography, heart rate, pulse oximetry, noninvasive blood pressure) and state entropy (SE) were monitored throughout the opera-

tion. After tracheal intubation, anesthesia was maintained with 1.2–2.4 vol% isoflurane or 6–12 vol% desflurane (end-tidal concentration) in 1.5 l/min nitrous oxide (N₂O), and 1.5 l/min O₂, depending on the vital signs and SE. Ventilation was controlled, and the end-tidal carbon dioxide tension (P_{ET} CO₂) was maintained within the range of 32–38 mmHg. Neuromuscular block was monitored with a peripheral nerve stimulator, and additional increments of vecuronium were administered if the train-of-four count was more than one twitch. The concentrations of isoflurane, desflurane, N₂O, and CO₂ were measured continuously using an anesthetic gas monitoring system (S/5™ Compact anesthesia monitor; Datex-Ohmeda, Tewksbury, MA, USA). The lower limits of sensitivity for isoflurane and desflurane were 0.01% and 0.1%, respectively.

To control postoperative pain, intravenous patient-controlled analgesia (PCA, Automed 3300™, AceMedical Co., Seoul, S. Korea) was used to administer fentanyl. The mode of PCA was a continuous infusion of 0.125 μ g/kg/h with boluses of 0.125 μ g/kg and a lockout interval of 15 min (total regimen 100 ml).

At the point when the operation was predicted to end in an hour, the isoflurane dose was reduced to 1 minimum alveolar concentration (MAC, 1.2% end-tidal concentration in isoflurane) in Group I, the desflurane dose was reduced to 1 MAC (6% end-tidal concentration in desflurane) in Group D, or the isoflurane was replaced with 1 MAC of desflurane in Group X [6]. Spontaneous ventilation was established before starting skin closure. Isoflurane or desflurane and N₂O were discontinued immediately after the skin closure. The patients' lungs were then ventilated with 100% O₂ at a total gas flow rate of 5 l/min. Patients' breathing was maintained under assisted ventilation before discontinuation of inhalation anesthetics, and under spontaneous ventilation after discontinuation of inhalation anesthetics. The patients' tracheae were extubated after the reversal of neuromuscular blockade with a combination of 10–15 mg pyridostigmine and 0.2–0.4 mg glycopyrrolate. After extubation patients were transferred to the PACU and a blinded investigator recorded the recovery variables. At PACU, if the patients expressed prolonged pain of over 30 mm on the VAS, they were given an intravenous injection of 50 μ g fentanyl as rescue analgesia

until the pain was relieved ($VAS < 30$ mm).

Recovery profile. After discontinuation of the inhalation anesthetic, the time required for the end-tidal concentration of the volatile anesthetic to reach 50% of the concentration at its termination was recorded. The response time to painful pinching and verbal command, and to regain orientation to age and name were assessed in a uniform manner at 1 min intervals after inhalation anesthetic was discontinued.

Patients were asked to complete the following psychometric tests in the day before surgery and then 30 and 60 min after discontinuation of anesthetics: 1) a digit symbol substitution test (DSST: in which patients are asked to match numbers and symbols during a 90-s period to measure cognitive ability)[10]; 2) a serial 7 test (SST: in which patients are asked to subtract 7 continuously from 100 and the time to reach the last number is measured)[11]. Patients were discharged from PACU according to our local score, derived from the Aldrete score [12].

The primary outcome measure of this study was the response time to appropriate verbal command. Secondary outcome measures included: the response time to painful pinching, regaining orientation to age and name, time to fitness for discharge from PACU, DSST and SST.

Consumption of inhalation anesthetics was calculated using the equation presented by Weiskopf and Eger, [5] and the costs of consumed inhalation anesthetic were calculated based on our hospital pharmacy list. The exchange rate from the Korean won to the United States dollar was 1 dollar = 1103.20 won.

Statistical analysis. To calculate the required sample size for the study, the difference in recovery times between isoflurane and desflurane anesthesia reported in a similar clinical setting was considered [1]. We accepted a two-tailed α error of 5% and a β error of 10% to detect a 2-min difference among the 3 groups with regard to the time taken to open eyes in response to the appropriate verbal command. Based on these calculations, the required sample size for the study was 26 per group. To compensate for a patient refusal rate of 20% and a dropout rate of 5%, we asked 103 patients to participate in the study.

For intergroup comparisons, ANOVA with the Tukey post hoc test was used to compare the continuous variables in the three treatment groups. The shifts from the baseline values and systematic differ-

ences in the hemodynamic variables, inhalation concentration, $P_{ET}CO_2$, and psychometric test results were analyzed between the 3 groups by a repeated measures analysis of variance (ANOVA) followed by a simple contrast. The descriptive variables were analyzed by either by chi-square analysis or Fisher's exact test, as appropriate. P values of < 0.05 were considered statistically significant.

In the Table, data are presented as mean \pm standard deviation if normally distributed, and if not as median (interquartile range) or absolute values. In the Figure, data are presented mean values with variability expressed as standard error. Statistical analysis was performed with SPSS version 15.0 (SPSS, USA).

Results

Among the 103 patients who were asked to participate in the study between Sep 2008 and Oct 2009, 13 patients refused to participate and 8 patients were excluded as they suffered from cardiac, pulmonary, renal, or neurologic disease or were chronic users of drugs, both of which are known to affect anesthetic requirements. Of the 82 patients, 27 were randomized to Group I, 29 to Group D, and 26 to Group X.

As shown in Table 1, there were no significant differences in the demographic data. The duration of anesthesia, operation, and cross-over period and the number of patients who required medication intraoperatively and postoperatively did not differ (Table 2). Hemodynamic variables in the 3 groups did not differ before the reduction or change in the inhalation anesthetic (baseline), and there were no systematic differences after reductions or changes in the anesthetics (Figs. 1A, 1B).

MAC did not differ systematically among groups, and did not differ from baseline at any time in Group I and Group D: however MAC was significantly higher than baseline from 5 min to 10 min in Group X ($p < 0.05$, Fig. 2A). MAC of desflurane and isoflurane, and the sum of MAC in Group X are presented in Fig. 2B. SE was significantly lower than the baseline from 5 min to 20 min in Group X ($p < 0.05$), but did not differ from baseline at any time in Group I and Group D (Fig. 3).

The patients in Group D responded to painful pinching, opened their eyes to the appropriate verbal

Table 1 Demographic data and times

	Group I (n = 27)	Group X (n = 26)	Group D (n = 29)
Age; years	61.0 (58.0–68.0[18–65])	59.5 (48.8–66.5[18–65])	64.0 (53.5–72.5[18–65])
Gender M	17 (63.0)	16 (61.5)	15 (51.7)
F	10 (37.0)	10 (38.5)	14 (48.3)
Height; cm	166.1(6.9)	165.4 (7.3)	161.6 (7.9)
Weight; kg	63.9 (8.7)	63.5 (8.3)	61.0 (6.8)
ASA I	14 (51.9)	14 (53.8)	14 (48.3)
II	11 (40.7)	11 (42.4)	14 (48.3)
III	2 (7.4)	1 (3.8)	1 (3.4)
Cross-over time; min	67.2 (13.5)	62.5 (12.6)	63.0 (11.2)
Op time; min	224.9 (83.7)	220.4 (75.8)	250.7 (76.7)
Ane time; min	246.4 (82.6)	237.2 (71.4)	275.8 (88.7)

Values are median (IQR[Range]), mean (SD), and number (proportion). No significant differences among groups. ASA, American Society of Anesthesiologists physical status; Op, operation; Ane, anesthesia.

Table 2 Additional drug requirement

	Group I (n = 27)	Group X (n = 26)	Group D (n = 29)	P-value
Intra OP				
Glycopyrrolate	2 (7.4)	3 (11.5)	2 (6.9)	0.801 †
Ephedrine	2 (7.4)	2 (7.6)	2 (6.9)	0.993 †
Fentanyl	10 (37.0)	10 (38.5)	12 (41.4)	0.944
Vecuronium (mg)	14.9 (2.3)	14.8 (2.6)	14.6 (2.2)	0.914
Post OP				
Fentanyl	8 (29.6)	9 (34.6)	11 (37.9)	0.806
Ondansetron	9 (33.3)	7 (26.9)	9 (31.0)	0.877

Values are mean (SD), and number (proportion). No significant differences among groups. OP, operation. † Fisher's exact test was used.

command, regained orientation to name and reached the fitness for discharge from PACU earlier than those in Group I ($p < 0.05$) and the patients in Group X responded to verbal command and reached the fitness for discharge from PACU earlier than those in Group I ($p < 0.05$), but there were no difference between Group X and Group D (Table 3). After discontinuation of volatile anesthetic, the time required for the end-tidal concentration of the volatile anesthetic to reach 50% of its termination value was significantly less in Group X and Group D than in Group I ($p < 0.001$), but there were no significant differences between Group I and Group D (Table 3).

Five patients in Group I, 3 in Group X, and 3 in Group D at 30 min and 2 patients in Group I, 2 in Group X, and 2 in Group D at 60 min could not perform DSST and SST because of severe pain. In

addition, 5 patients in Group I, 2 in Group X, and 2 in Group D at 30 min and 6 patients in Group I, 1 in Group X, and 1 in Group D at 60 min could not perform DSST and SST because they sleep without interruption. Patients who could not perform DSST and SST were excluded from the analysis. There were no differences in the DSST and SST before the surgery; patients performed significantly better in Group X and Group D than Group I at 30 and 60 min after admission to the PACU ($p < 0.05$). However, the DSST and SST scores at 30 and 60 min differed significantly from before the surgery ($p < 0.05$, Table 4).

The cost of consumed inhalation anesthetics was higher in Group D than in Group X and Group C ($p < 0.05$), and higher in Group X than in Group C ($p < 0.05$, Table 5).

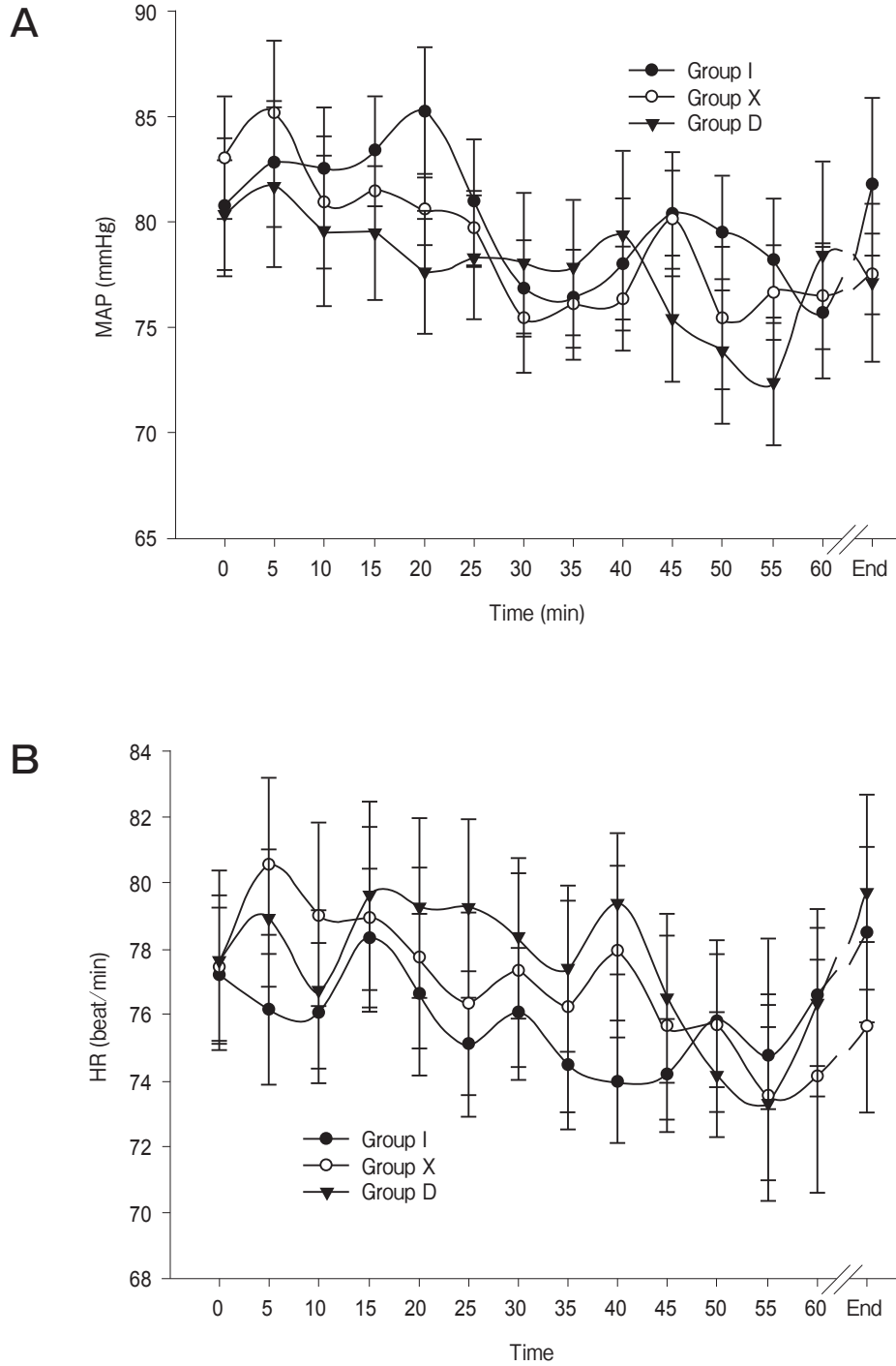


Fig. 1 **A**, Changes in mean arterial pressure during the cross-over period. Each line represents mean \pm SE; **B**, Changes in heart rate during the cross-over period. Each line represents mean \pm SE. 0, beginning of cross-over; End, end of operation.

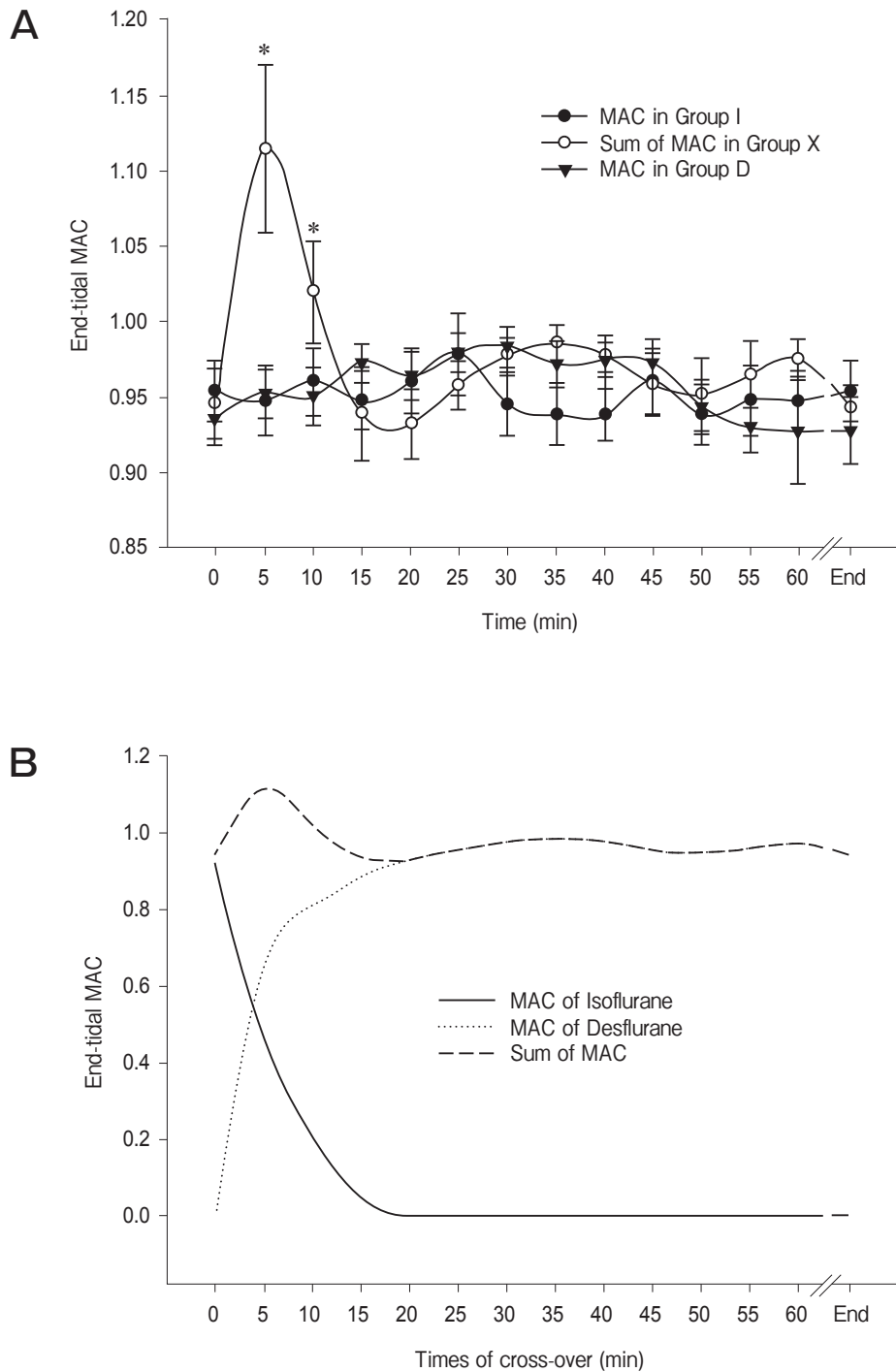


Fig. 2 **A**, End-tidal MAC of inhalation agent during the cross-over period. Group X represents the sum of MAC in isoflurane and desflurane. Each line represents the mean \pm SE. * $P < 0.05$ within group in comparison with baseline value; **B**, End-tidal MAC of inhalation agent during the cross-over period in Group X. 0, beginning of cross-over; End, end of operation.

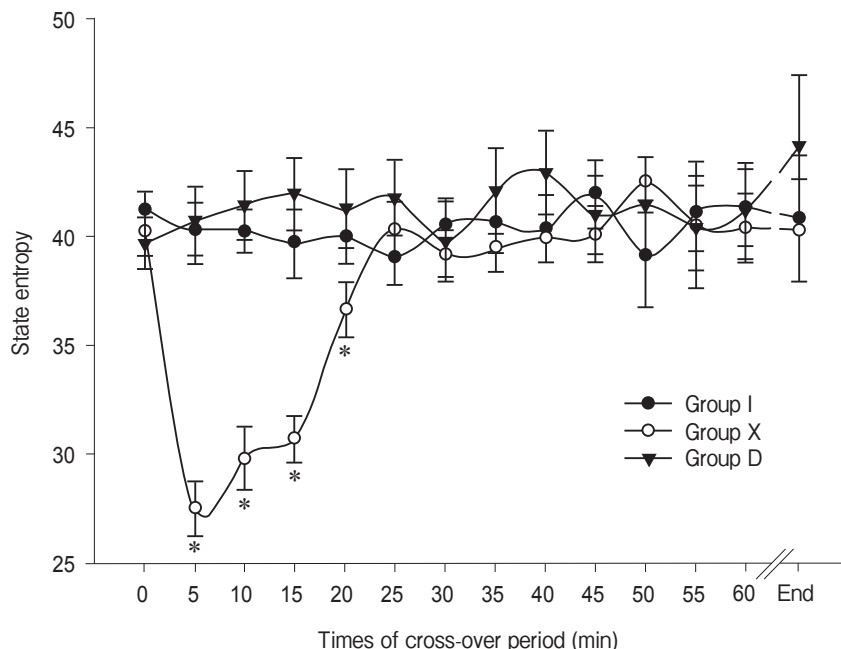


Fig. 3 State entropy during the cross-over period. Each line represents the mean ± SE. *P < 0.05 within group in comparison with baseline value. 0, beginning of cross-over; End, end of operation.

Table 3 Emergence and recovery characteristics

	Group I (n = 27)	Group X (n = 26)	Group D (n = 29)	P-value
T 50% dec; sec	100 (80-150[45-180])	50 (43-57.3[35-120])*	60 (55-70[45-110])*	<0.001
Painful pinch; min	25.2 (13.0)	20.5 (10.7)	19.1 (8.9)*	0.036
Verbal command; min	29.4 (7.6)	22.9 (11.6)*	20.3 (9.3)*	0.002
Age; min	36.1 (9.7)	29.2 (13.9)	28.1 (13.0)	0.039
Name; min	35.6 (9.1)	29.0 (13.8)	28.0 (12.6)*	0.046
PACU discharge; min	47.2 (9.3)	39.4 (12.5)*	37.3 (10.8)*	0.003

Values are median (IQR[Range]), mean (SD), number (proportion). *P < 0.05 compared with group I, There were no differences between group X and group D. T 50%, the time required for the end-tidal concentration of the volatile anesthetic to reach 50% of the concentration at its termination, PACU, Post Anesthetic Care Unit.

Discussion

Our findings support the hypothesis that when anesthetized patients undergo laparotomy lasting 3 or more hours, changing from isoflurane to desflurane anesthesia results in earlier emergence and recovery than pure isoflurane anesthesia, and nearly equal emergence and recovery with desflurane anesthesia. In agreement with other studies [1, 13], we also found that emergence and recovery after desflurane is more

rapid than that after the more soluble isoflurane.

As a primary outcome measure, the time to open eyes to the appropriate verbal command was earlier in Group X and Group D than in Group I. Additionally, Group X and Group D performed better postoperatively in both the SST and DSST than Group I. Considering that more patients cannot perform DSST and SST postoperatively, these differences may be potentiated. These differences in emergence and recovery profiles were not caused by differences in the

Table 4 Psychometric test

	Group I (n = 27)	Group X (n = 26)	Group D (n = 29)	P-value
DSST-0	44.04 ± 5.57	43.50 ± 5.01	43.34 ± 4.46	0.866
DSST-30	19.12 ± 9.5 †	28.14 ± 10.00* †	28.54 ± 8.80* †	0.004
DSST-60	32.76 ± 7.01 †	40.57 ± 6.95* †	40.35 ± 5.74* †	0.003
SST-0	64.37 ± 11.30	63.58 ± 12.06	64.59 ± 11.53	0.945
SST-30	123.94 ± 31.29 †	99.76 ± 35.46* †	91.79 ± 25.31* †	0.006
SST-60	84.00 ± 18.94 †	70.48 ± 12.91* †	71.81 ± 9.20* †	0.003

Values are mean (SD). Number of patients is 17, 21, 24 at 30 min, 21, 23, 26, at 60 min in Group I, Group X, and Group D respectively. * $P < 0.05$ compared with group I, There were no differences between group X and group D. † $P < 0.05$ compared with before surgery. DSST, digit symbol substitution test; SST, Serial 7 test. -0, -30, -60; performed before surgery, 30, and 60 min postoperatively.

Table 5 Comparison of costs

	Group I (n = 27)	Group X (n = 26)	Group D (n = 29)	P-value
Volume of anesthetic used				
Isoflurane	74.3 (10.4)	68.8 (9.0)		
Desflurane		66.4 (3.1)	269.0 (13.2)	
Cost of anesthetic				
Isoflurane	46.8 (6.6)	43.2 (5.7)		
Desflurane		43.3 (10.5)	175.6 (46.5)	
Sum	46.8 (6.6)	86.7 (14.4)*	175.6 (46.5)* †	<0.0001

Values are mean (SD). Costs were calculated based on our institution's pharmacy list (Isoflurane 250ml = 157.40 United States Dollar, desflurane 240ml = 156.7 United States Dollar) and are expressed in United States dollars. * $P < 0.05$ compared with group I, † $P < 0.05$ between group X and group D.

duration of anesthesia, cross-over period, or dose of used muscle relaxant and opioid, since none of these parameters were significantly different. They were also not caused by differences in anesthetic concentrations (MAC) or alveolar ventilation during recovery, which was assessed by the end-tidal concentrations of anesthetics and CO₂: these parameters also did not differ among groups. The pharmacokinetic data reinforce these clinical results. The time required for the end-tidal concentration of the volatile anesthetic to reach 50% of its termination value was significantly less with desflurane and with changing from isoflurane to desflurane anesthesia than with pure isoflurane anesthesia. It is somewhat predictable that desflurane with a blood/gas partition coefficient of 0.42, compared with 1.4 in isoflurane, washed out at a much faster rate resulting in faster emergence and recovery [4, 14]. The times to respond to painful pinch and to regain orientation to age and name were not significantly different between Group X and Group I (Table

3). The reason for this lack of difference may be that these parameters were not the primary criterion. As we made the reliable group number by calculating the time taken to open eyes in response to the appropriate verbal command, the number of patients in the current study might be small to provide statistically significant results for these emergence and recovery parameters.

These results are in close agreement with those of our previous study, which showed that changing from enflurane to desflurane results in an earlier emergence and recovery profile compared with pure enflurane anesthesia, although different anesthetics and protocols were used [9]. However, our findings are different from those of Neumann *et al.* [7], who compared the recovery after desflurane anesthesia, isoflurane anesthesia, and changing from isoflurane to desflurane anesthesia in 5 volunteers. Changing from isoflurane to desflurane in their study produced similar results with regard to the response times to a command, orientation, and cognitive performance, as those

observed with isoflurane alone. We postulate that these differences between the 2 studies result from the difference in the duration of anesthesia (2 h vs. 3 h), duration of the cross-over period (30 min vs. 1 h), study subjects (5 volunteers vs. 82 patients), and rate of fresh gas flow (2 l/min vs. 3 l/min).

The time to fitness for discharge from PACU was earlier in Group X and Group D than in Group I. Although the clinical significance of less than 5 min in the time to readiness to leave PACU between Group X and Group I may be questioned, even small differences in times to leave PACU, we assume, may translate into significant cost- and labor-savings in a busy PACU [15, 16]. However, a more detailed cost-benefit analysis may be needed to confirm this assumption.

In the semi-closed system commonly used, changing isoflurane to desflurane will not cause the rapid elimination of isoflurane from the circuit and will cause rebreathing of isoflurane exhaled by the patients. A delayed elimination of isoflurane will result. In addition, because desflurane is less soluble, the circuit and alveolar concentrations of desflurane will increase more rapidly than the concentrations of isoflurane will decrease. Therefore, the sum of MAC for each anesthetic in Group X increased significantly at 5, 10 min after cross-over started (Fig. 2A, 2B), which is reflected in the lower SE than baseline value from 5 min to 20 min after the start of the cross-over (Fig. 3). Although the decrease in SE lasted longer than the duration of the increase in MAC, we assume that these differences may be caused by end-tidal concentrations of isoflurane during the cross-over, which were maintained below the lower limits of sensitivity, or that the interaction between the 2 anesthetics impeded their detection by infra-red gas analyzer. We assume that different results may arise if gas chromatography is used. The possibility that temperature, N₂O, and pH may affect this inconsistency also cannot be ruled out.

Rapid emergence may improve airway protection after tracheal extubation in the PACU, and early recovery (such as response to external stimulus, orientation to age and name) can protect patients from accident often less supervised at this time and improve postoperative management and cost- and labor-savings in a busy PACU. To achieve such advantages in early emergence and recovery, desflurane is most suitable

for maintaining anesthesia. However, desflurane is more expensive than isoflurane, because its cost is relatively high and its high MAC causes a consumption of desflurane. In this study, the cost of consumed inhalation anesthetics was lower in Group X than in Group D, and emergence and recovery were earlier in Group X than in Group I. Thus, we can achieve twin goals of economy and rapid recovery using the sequential technique (isoflurane to desflurane). Further, quicker recovery of cognitive function and earlier discharge from the PACU to a normal ward may reduce staff costs [15, 16].

The main disadvantages of changing from isoflurane to desflurane anesthesia are the activation of the sympathetic nervous system caused by rapid increases in inspired desflurane concentrations, and increases in the depth of anesthesia caused by disagreements in rate between the elimination of isoflurane and the uptake of desflurane. In group X, MAP and HR increased at 5 min after the change of anesthetics (Fig. 1A, 1B), which may have been caused by activation of the sympathetic nervous system [17]. However this increase did not reach statistical significance, possibly because the residual isoflurane offset the sympathetic nervous system activation caused by desflurane. Increase in the depth of anesthesia was reflected in an increase in MAC from 5 min to 10 min, and a decrease in SE from 5 min to 20 min (Fig. 3). This discrepancy in time between increase in MAC and decrease in SE may possibly deliver more anesthetic than necessary to achieve adequate anesthesia. Accordingly, it may reduce the benefit from the decreased cost of consumed anesthetics.

The present study does have some limitations. First, to standardize the anesthetic for this study, the volatile agent was maintained at 1 MAC until the end of surgery. Most anesthesiologists do not practice in this fashion. Instead, they decrease the fraction of inhaled anesthetic agent as the anticipated end of surgery approaches. This approach might compensate for an expected difference between isoflurane and crossover from isoflurane to desflurane in daily practice.

Second, despite the rigid protocol, there remain a large number of confounding factors that introduce potential errors into the observation. These include different operation, surgeons, and patient characteristics. It is difficult to account for all these confound-

ing factors and our protocol was designed to minimize them as much as possible. Third, the observers in the operating room were not blinded. This could have added bias to the results, accentuating or diminishing differences among the three groups. Finally, a fresh gas flow of 3l/min leads to greater anesthetic consumption compared with a low-flow system. This increased consumption would increase costs and decrease the economic benefit from changing anesthetics. However, the total cost of anesthetic used when changing from isoflurane to desflurane may be lesser than pure desflurane anesthesia.

In conclusion, we found that changing anesthetics from isoflurane to desflurane during the last 1 h of anesthesia during laparotomy that lasted for 3 h or longer improved emergence and recovery.

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