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Recovery Profile after Desflurane–Nitrous Oxide Versus *Isoflurane–Nitrous Oxide in Outpatients*

Ahmed F. Ghouri, Matthew Bodner, M.D.,† Paul F. White Ph.D., M.D.‡*

Thirty-eight healthy outpatients undergoing elective surgical procedures lasting 1–3 h were randomly assigned to receive either desflurane 3% (approximately 0.5 MAC) or isoflurane 0.6% (approximately 0.5 MAC) for maintenance of general anesthesia with nitrous oxide 60% in oxygen after a standardized induction sequence consisting of fentanyl 3 $\mu g \cdot kg^{-1}$, thiopental 4 $mg \cdot kg^{-1}$, and succinylcholine 1–1.5 $mg \cdot kg^{-1}$, intravenously. Although anesthetic conditions were similar during operations in the two treatment groups, significant differences were noted in the recovery profiles as measured by elimination kinetics, psychometric testing, and visual analog scales (to assess subjective feelings). The time required for the end-tidal concentration to decrease by 50% was 2.5 ± 0.8 min for desflurane *vs.* 9.5 ± 3.4 min for isoflurane (mean ± standard deviation [SD]). Times to awakening and ability to follow simple commands were significantly shorter after desflurane than after isoflurane (5.1 ± 2.4 *vs.* 10.2 ± 7.7 min 6.5 ± 2.3 min *vs.* 11.1 ± 7.9 min, respectively). Postoperatively, patients who received desflurane exhibited less impairment of cognitive function (as measured using the Digit–Symbol Substitution Test) than did those who received isoflurane. Furthermore, visual analog scores indicated that patients receiving desflurane experienced significantly less discomfort (pain), drowsiness, fatigue, clumsiness, and confusion in the early postoperative period. We conclude that desflurane may offer clinical advantages over isoflurane when used for maintenance of anesthesia during outpatient surgical procedures. (Key words: Analgesics, opioid: fentanyl. Anesthetic technique: inhalational. Anesthetics, volatile: desflurane; isoflurane. Anesthetics, gas: nitrous oxide. Recovery test: analog scales; Digit–Symbol Substitution Test (DSST); Trieger test.)

INHALED VOLATILE ANESTHETICS remain the most widely used drugs for maintenance of general anesthesia in the outpatient setting because of their ease of administration and predictable intraoperative and recovery characteristics. A study by Valanne and Korttila suggested that isoflurane, the least soluble of the available volatile agents, was associated with a more rapid spontaneous recovery than was enflurane after procedures lasting longer than 90 min.[1] Desflurane, a new volatile anesthetic, is less soluble than other currently available inhalational agents.[2] Consequently, its rapid elimination from the brain would be expected to result in an improved recovery profile after ambulatory (outpatient) surgical procedures.[3,4]

This study was designed to compare the emergence and recovery characteristics of outpatients receiving either desflurane or isoflurane with nitrous oxide for the maintenance of general anesthesia after a standardized induction technique. Recovery of cognitive and psychomotor function was evaluated with the Digit–Symbol Substitution Test (DSST) and the Trieger test, respectively, and subjective assessments were measured with standardized visual analog scales.

Materials and Methods

Thirty-eight healthy (ASA Physical Status 1 or 2) outpatients scheduled for elective surgical procedures were studied according to a protocol approved by the Human Studies Committee at the Washington University School of Medicine. Written informed consent was obtained from all patients. Operations included diagnostic arthroscopy (40%), superficial general surgery (24%), plastic surgery (23%), and diagnostic laparoscopy (13%).

Patients were randomly assigned to either the isoflurane or desflurane treatment group according to an open (nonblinded) study design. Patients with clinically significant pulmonary, cardiovascular, hepatic, renal, hematologic, neurologic, or metabolic diseases were excluded from participation in the study. Also excluded were patients with a history of allergic reactions to any of the study drugs, those who chronically used drugs known to affect anesthetic (or analgesic) requirements, and those who had had general anesthesia within 7 days prior to the study.

Patients received no preanesthetic medication. Upon arrival in the preanesthetic holding area, patients were asked to complete the following baseline psychometric tests: 1) a Trieger test (in which patients are asked to connect a series of dots to evaluate psychomotor function)[5]; 2) linear visual analog scales (to assess the degree of subjective impairment)[6,7]; and 3) a DSST (in which patients are asked to match numbers and symbols during a 90-s period to measure cognitive ability).[8,9] The visual analog scales were used to assess discomfort (pain), drowsiness, fatigue, clumsiness, and confusion.

During the operation, routine monitoring devices included a precordial stethoscope, esophageal temperature probe, ECG, pulse oximeter (Ohmeda Biox,™ Boulder, CO), and vital signs monitor (Critikon Dinamap,™

* Medical Student; Research Associate.
† Instructor.
‡ Professor; Director of Clinical Research.
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Address reprint requests to Dr. White: Department of Anesthesiology, Washington University School of Medicine, Box 8054, 660 South Euclid Avenue, St. Louis, Missouri 63110.

Tampa, FL). The inspired O_2 and end-tidal concentrations of N_2O, isoflurane, desflurane, and CO_2 were measured continuously with a specially designed infrared gas analyzer (Datex,® Puritan Bennett, Tewksbury, MA). The monitor was calibrated prior to each surgical procedure with the use of gases analyzed to ±0.02% accuracy (Scott Medical Products, Plumsteadville, PA). The lower limit of sensitivity for desflurane was 0.1%. Hemodynamic and respiratory variables were recorded at 1-min intervals for 5 min after surgical incision. Subsequent measurements were performed at 5-min intervals until the end of the operation.

The general anesthetic technique consisted of fentanyl 3 $\mu g \cdot kg^{-1}$ intravenously (iv) and a defasciculating dose of *d*-tubocurarine, 2–3 mg iv, administered over 3–5 min prior to induction of anesthesia with thiopental 4 $mg \cdot kg^{-1}$ iv. Succinylcholine 1–1.5 $mg \cdot kg^{-1}$ iv was administered to facilitate tracheal intubation. In the control group, anesthesia was maintained with isoflurane 0.6% end-tidal and N_2O 60% in O_2 (3 $l \cdot min^{-1}$/2 $l \cdot min^{-1}$), and the treatment group received an initial end-tidal concentration of desflurane 3.0% end-tidal and N_2O 60% in O_2 (3 $l \cdot min^{-1}$/2 $l \cdot min^{-1}$). In addition, vecuronium 1–3 mg iv was administered to both groups as needed to maintain adequate surgical relaxation. Ventilation was controlled and end-tidal CO_2 tension (PET_{CO_2}) was maintained in the range of 32–38 mmHg.

Increases in heart rate and blood pressure (exceeding 20% of baseline) that did not respond to increases of 25–50% (of initial value) in the inspired concentrations of the inhaled agent were treated with fentanyl 25–50 μg iv bolus doses, as needed. Similarly, decreases in heart rate or blood pressure that did not respond to decreases in the inspired concentration of the inhaled agent by 25–50% were treated with atropine 0.2–0.4 mg iv or ephedrine 5–10 mg iv, respectively.

At the end of the operation, residual neuromuscular blockade was reversed with a combination of neostigmine 3–5 mg iv and glycopyrrolate 0.6–1.0 mg iv. Isoflurane and desflurane were discontinued at the time of skin closure, and N_2O was discontinued immediately after skin closure. Patients' lungs then were ventilated with 100% O_2 at a total gas flow rate of 5 $l \cdot min^{-1}$, and PET_{CO_2} was maintained at 35 ± 2 mmHg. After discontinuation of the agents, expired concentrations of the inhaled agents were recorded at 30-s intervals until they were no longer detectable (<0.1%) in the expired gases. The times at which the patient spontaneously opened his or her eyes and was able to follow the command to squeeze the investigator's hand were recorded. Ability to follow commands was assessed at 15–30-s intervals after spontaneous eye opening. Postoperatively, antiemetics (*e.g.*, metoclopramide 5–20 mg iv) were administered for nausea and vomiting, and opioid analgesics (*e.g.*, morphine 2–4 mg iv and meperidine 25–50 mg iv) were given for moderate-to-severe pain. A research nurse who was blinded as to the volatile anesthetic agent used in the study recorded the times to sitting up in a chair, to being transferred from the phase 1 to the phase 2 recovery unit, and to being judged ready for discharge.

At 30, 60, and 90-min intervals after entry into the Postanesthesia Care Unit (PACU), visual analog scales, as well as the Trieger test and DSST, were repeated by a trained research nurse blinded as to the anesthetic technique used during the operation. The Trieger test was scored according to the number of dots missed, and the DSST by the number of symbols completed and correctly matched. The visual analog scales consisted of five 100-mm lines, representing discomfort (pain), drowsiness, fatigue, clumsiness, and confusion, with 0 = minimal impairment and 100 = maximal impairment (*e.g.*, on the discomfort scale, 0 = no pain and 100 = severe pain; on the drowsiness scale, 0 = fully awake and alert and 100 = extremely sleepy).

Data are reported as mean values, with variability expressed as either standard deviation (SD) in the tables or standard error of the mean (SEM) in the figures. Statistical analysis was performed with the FASTAT data analysis system (Systat, Inc., Evanston, IL). Psychometric test results were analyzed by analysis of variance with respect to changes over time (as compared to the preoperative baseline value), and differences between the two treatment groups were analyzed by the Student's *t* test. Descriptive variables were analyzed by chi-squared analysis or Fisher's exact test when appropriate; P values < 0.05 were considered statistically significant.

Results

The two treatment groups were comparable with respect to age, weight, height, duration of anesthesia (table 1), and types of surgical procedures performed. In ad-

TABLE 1. Patient Demographic Characteristics and Adjunctive Drug Requirements

	Isoflurane	Desflurane
Number (n)	21	17
Sex (M/F)	7/14	9/8
Age (yr)	40 ± 14	44 ± 11
Weight (kg)	74 ± 16	83 ± 16
Height (cm)	172 ± 9	169 ± 11
Duration of anesthesia (min)	127 ± 80	98 ± 55
Initial fentanyl dose ($\mu g \cdot kg^{-1}$)	3.1 ± 0.6	3.0 ± 0.5
d-tubocurarine dose (mg)	3.0 ± 0.2	3.0 ± 0.2
Succinylcholine dose ($mg \cdot kg^{-1}$)	1.4 ± 0.1	1.3 ± 0.6
Total thiopental dose ($mg \cdot kg^{-1}$)	4.4 ± 1.5	4.2 ± 0.9
Total fentanyl dose ($\mu g \cdot kg^{-1}$)	4.0 ± 1.4	3.5 ± 0.9
Total vecuronium dose ($mg \cdot kg^{-1}$)	0.07 ± 0.05	0.05 ± 0.03

Mean values ± SD.

dition, there were no significant differences in the total doses of thiopental, succinylcholine, fentanyl, or vecuronium administered during the operations. The number of intraoperative and postoperative events requiring pharmacologic intervention in the two treatment groups also were similar (table 2).

After discontinuation of the volatile agent, patients in the desflurane group opened their eyes and were able to follow commands significantly earlier than those in the isoflurane group. In addition, the time required for the end-tidal concentration of the volatile anesthetic to reach 50% of its termination value was significantly shorter after desflurane than after isoflurane (table 3). However, there were no statistically significant differences in the times to sitting up in a chair, to being transferred from phase 1 to phase 2 recovery, or to being judged ready for discharge (table 3).

A comparable number of patients in the desflurane and isoflurane groups required parenteral analgesic (8 of 17 *vs.* 11 of 21 patients, respectively) and antiemetic (6 of 17 *vs.* 9 of 21 patients, respectively) therapy during their PACU stay. Among patients given analgesic or antiemetic drugs, no differences were reported between the desflurane and isoflurane treatment groups in their average dose requirements (morphine equivalents: 4.2 ± 1.1 *vs.* 5.1 ± 0.8 mg, respectively and metoclopramide: 8.6 ± 1.6 *vs.* 9.6 ± 0.9 mg, respectively). At 30 min postoperatively, 12 of 21 (57%) in the group receiving isoflurane were unable to perform the psychometric tests because of nausea, fatigue, or pain. However, only 4 of 17 (24%) patients receiving desflurane were unable to complete the same tests and questionnaires ($P < 0.05$). At 60 and 90 min postoperatively, the difference in the two groups' ability to complete the psychometric testing was no longer statistically significant (86 and 81% in the isoflurane group *vs.* 89 and 89% in the desflurane group, respectively).

There were significant differences in the variables assessed with the visual analog scales (figs. 1 and 2) and in the results of the DSST (fig. 3) at 30, 60, and 90 min after arrival in the PACU. Consistently, patients in the desflurane group demonstrated a lesser degree of impairment on both subjective and objective tests than those in the isoflurane group. However, there were no differences between the two groups with regard to the number of missed dots on the Trieger test during the early postoperative period (fig. 4).

TABLE 2. Number of Adverse Intraoperative Cardiovascular Events and Side Effects in the PACU

Events	Isoflurane n = 21 (%)	Desflurane n = 17 (%)
Intraoperative*		
Tachycardia	3 (14)	0 (0)
Bradycardia	4 (19)	2 (12)
Hypertension	5 (26)	3 (18)
Hypotension	1 (5)	3 (18)
Postoperative (PACU)		
Nausea and vomiting	9 (43)	6 (35)
Pain	11 (52)	8 (47)

Given here are the numbers of cardiovascular events and side effects requiring pharmacologic intervention.
* Change in heart rate or blood pressure greater than 20% of the preinduction baseline value.

TABLE 3. Recovery Times after Discontinuation of the Inhaled Agent

	Isoflurane	Desflurane
End-tidal agent concentration at end of surgery (%)	0.6 ± 0.2	2.9 ± 0.4*
Time to 50% decrease in end-tidal concentration (min)	9.5 ± 3.4	2.5 ± 0.8*
Time to opening eyes (min)	10.2 ± 7.7	5.1 ± 2.4*
Time to following commands (min)	11.1 ± 7.9	6.5 ± 2.3*
Time to sitting up in a chair (min)	113 ± 27	95 ± 56
Time to phase 1 to 2 transfer (min)	118 ± 36	105 ± 49
Time to judged "home-ready" (min)	231 ± 40	207 ± 54

Mean values ± SD.
* Significantly different from isoflurane group, $P < 0.05$.

Discussion

Desflurane (formerly I-653) appears to offer some advantages over isoflurane with respect to emergence from anesthesia, time to orientation, and recovery of cognitive function when administered in equipotent concentrations[10–12] with 60% N_2O for the maintenance of general anesthesia in the outpatient setting.

Desflurane was eliminated more rapidly from the expired gases than isoflurane, as expected because of its lower tissue solubility. The observed half-lives for elimination of the two anesthetics were consistent with the kinetic differences recently reported by Jones *et al.* in healthy volunteers.[3] Although our "wash-out" kinetics were determined only at one end-tidal concentration, the study by Jones *et al.* suggested that similar kinetics exist at different end-tidal concentrations of desflurane. Furthermore, N_2O was not used as an adjuvant in their investigation.

In a preliminary study involving ten patients, Smiley and Ornstein compared the emergence from anesthesia after isoflurane and desflurane when administered with 60% N_2O.[4] They found mean times to awakening to be 10.6 min for desflurane and 13.4 min for isoflurane after surgical procedures lasting an average of 115 and 88 min, respectively. Although the duration of anesthesia was similar in both studies, the times to awakening were shorter in our study. Several important differences may explain this apparent discrepancy. First, Smiley and Ornstein studied a very small patient population (n = 5 per group). Second, their average maintenance concentrations

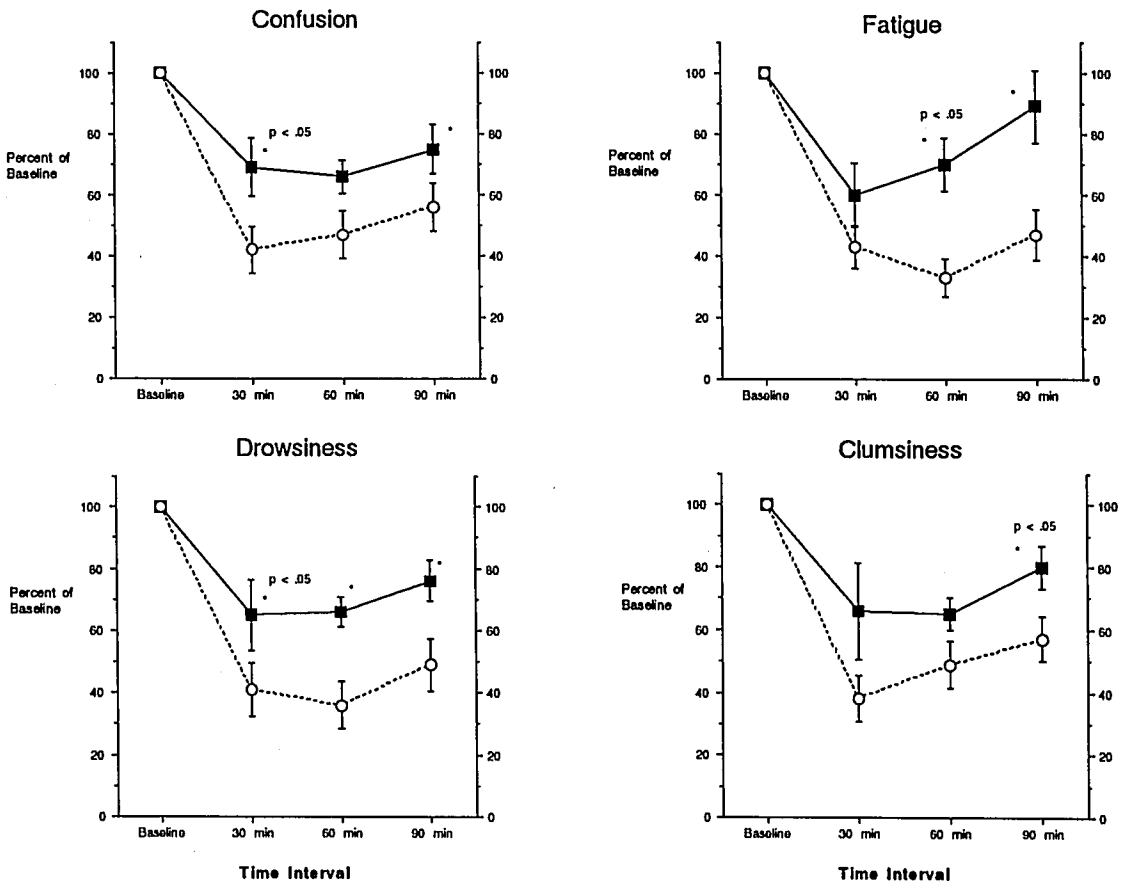

FIG. 1. Comparative visual analog scores for confusion, fatigue, drowsiness, and clumsiness demonstrated a more rapid return toward baseline values after desflurane (squares, solid line) compared to isoflurane (circles, dashed line). An asterisk denotes significant difference between the two treatment groups, a P value < 0.05.

of the volatile anesthetics were significantly higher than ours (4.7% desflurane and 0.8% isoflurane *vs.* 2.9% and 0.6% in our study). Finally, fentanyl (an opioid analgesic with volatile anesthetic-sparing effects)[13] was not administered to their patients, and the use of opioid analgesics to supplement inhaled anesthetics is known to facilitate emergence from general anesthesia.[14] For desflurane anesthesia, concomitant administration of opioid compounds is recommended because in the absence of adequate analgesia, rapid emergence has been associated with delirium.§ This delirium may be related to the fact that volatile anesthetics have been reported to antagonize opioid analgesic effects.[15]

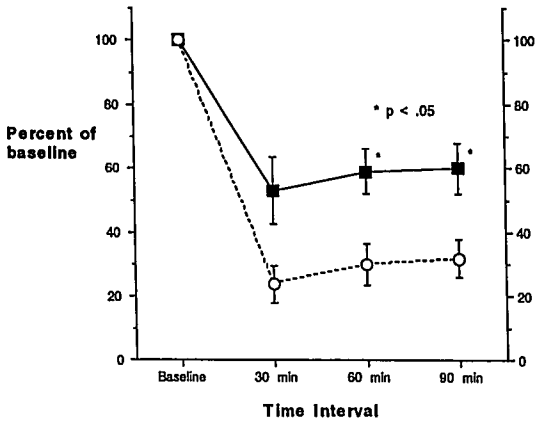

FIG. 2. Visual analog scores for comfort (pain) demonstrated a more rapid return toward baseline values after desflurane (squares, solid line) compared to isoflurane (circles, dashed line). An asterisk denotes significant difference between the two treatment groups, a P value < 0.05.

In addition to shorter emergence times, our results suggest that the use of desflurane (*vs.* isoflurane) is associated with less depression of cognitive function during the early postoperative period. In addition, the patients' subjective feelings of discomfort, drowsiness, fatigue, clumsiness, and confusion were more similar to their baseline values with desflurane as compared to isoflurane. These findings could not be explained by differences in the length of the operation, type of surgical procedure, or any other perioperative variable we examined.

It is important to mention that patients who could not complete the psychometric tests postoperatively were not

§ Damask MC: Personal communication. Anaquest, 1990.

included in our analysis. For example, only 43% in the isoflurane treatment group were able to perform the DSST at 30 min compared to 76% in the desflurane group. Therefore, the finding that the desflurane group performed better on this cognitive function test assumes even greater importance. Nevertheless, it should be emphasized that the mean scores on these psychometric tests did not return to their preoperative baseline values during the 90-min postoperative study period in either treatment group. Discharge times also were similar for the two treatment groups.

The slower elimination of isoflurane from brain tissue may explain the longer recovery times of isoflurane compared to desflurane. However, the difference in solubility characteristics of the two agents does not adequately explain why there were differences in patients' subjective feelings (*e.g.*, pain), since there were no significant differences in the amount of analgesic medication administered in the PACU. Indeed, it seems paradoxical that subjects who had a greater residual concentration of the anesthetic agent (isoflurane) reported more pain than did those who had a lower residual concentration, *i.e.*, those who were given desflurane, which is more rapidly eliminated. It is possible that some patients evaluated uncomfortable sensations (*e.g.*, nausea) as pain on the visual analog scales, which, in addition, are subject to intrinsic variability, as are the individual patient responses to postsurgical pain. Alternatively, residual desflurane may have exerted an analgesic effect (as has been suggested for N_2O[16,17]) that can potentiate the effect of opioid analgesics. It also is possible that low concentrations of isoflurane actually heighten the perception of pain (the "antanalgesic" effect).[15,18] Further studies are necessary to evaluate the possible explanations for this unexpected observation.

It is noteworthy that there were no significant differences in psychomotor performance (as measured by the Trieger test) and discharge times. Although test results of cognitive ability differed significantly between the groups, our assessment tool for recovery of psychomotor function may not have been sufficiently sensitive to detect a difference between the two anesthetic groups. Likewise, lack of significant differences in discharge times may reflect the postoperative testing procedure. All patients were required to remain in the same position on a gurney until after the 90-min tests were completed.

Finally, use of desflurane was not associated with an increased incidence of hemodynamic instability or other

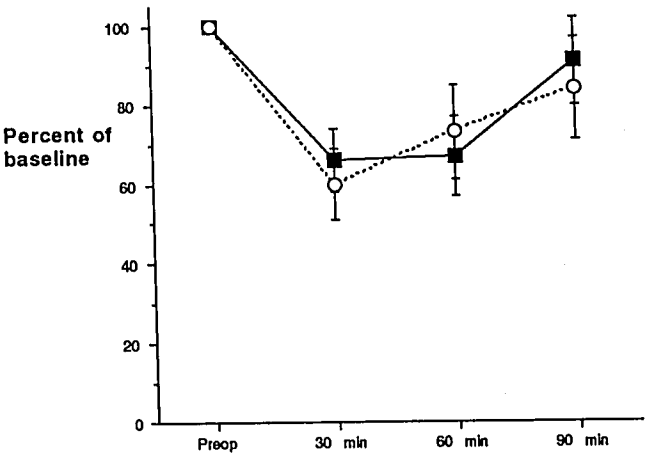

FIG. 4. Trieger test scores demonstrated no statistically significant differences between the desflurane (squares, solid line) and isoflurane (circles, dashed line) treatment groups with respect to psychomotor function at the time intervals tested.

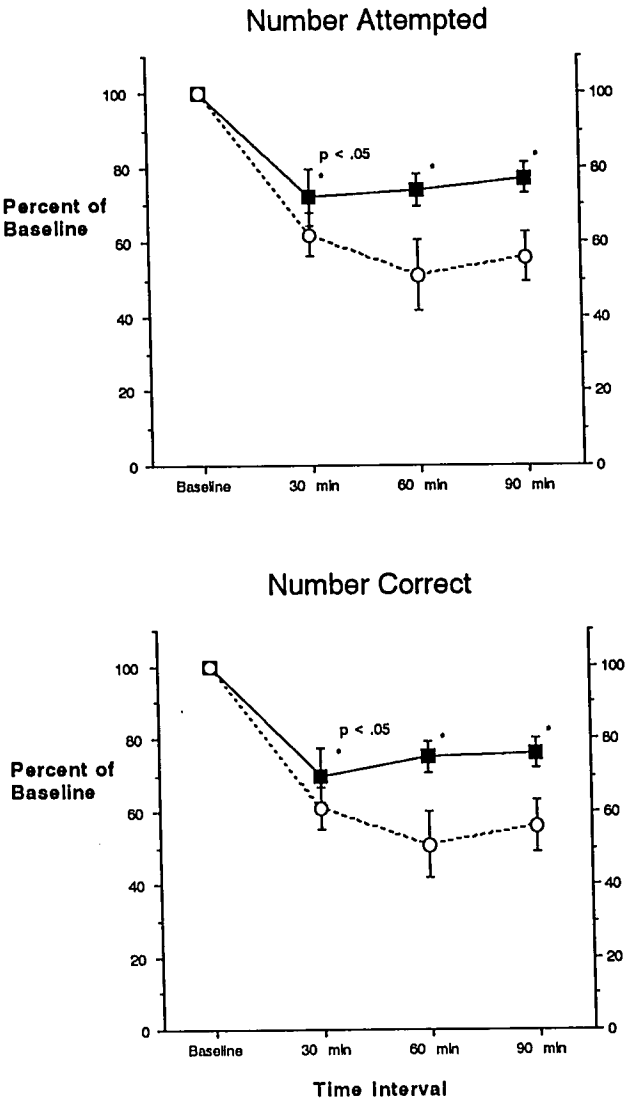

FIG. 3. Recovery of cognitive function, as assessed by the digit symbol substitution test (DSST), was more rapid in patients receiving desflurane (squares, solid line) compared to isoflurane (circles, dashed line). An asterisk denotes significant difference between the two treatment groups, a P value < 0.05.

adverse intraoperative events when used with N_2O and fentanyl for outpatient anesthesia. This result is consistent with previously published studies involving both humans[3,4] and laboratory animals.[19–21]

We conclude that desflurane may offer clinical advantages over isoflurane when administered for maintenance of anesthesia in situations where rapid emergence and recovery of cognitive function are important.

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