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ORIGINAL ARTICLE

Superior recovery profiles of propofol-based regimen as compared to isoflurane-based regimen in patients undergoing craniotomy for primary brain tumor excision: a retrospective study

Yoshihide Miura · Kouhei Kamiya · Kaoru Kanazawa · Masayuki Okada · Masaki Nakane · Airi Kumasaka · Kaneyuki Kawamae

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Abstract
Purpose Studies comparing the recovery profiles of isoflurane- and propofol-based anesthesia for major intracranial surgery have reported contradictory results. The aim of our study was to clarify the emergence status in both regimens by investigating uniformly managed neuroanesthesia cases.
Methods The anesthesia database at Yamagata University Hospital covering the period 2002–2005 was retrospectively investigated for adult patients who underwent craniotomy for primary brain tumor excision. General anesthesia was provided by an isoflurane- (ISO group) or propofol-based (PROP group) regimen. Times to extubation and operating room (OR) discharge, perioperative consciousness levels, and perioperative variables were compared.
Results Of the 202 surgeries performed during the study period, 77 and 82 patients were anesthetized with isoflurane and propofol, respectively. Demographic data were comparable between the two groups, although the American Society of Anesthesiology grade was worse in the PROP group. Extubation times [39.5 ± 14.6 min (ISO) vs. 29.5 ± 14.9 min (PROP); $P < 0.001$] and OR discharge times [67.2 ± 18.0 (ISO) vs. 53.9 ± 17.6 min (PROP); $P < 0.001$] were significantly shorter in the PROP, with significantly better immediate consciousness levels. The differences in levels of consciousness persisted for several hours postoperatively. PROP patients had significantly higher urine outputs and lower body temperatures during anesthesia. The incidences of shivering, nausea, vomiting, and convulsions were not significantly different between the groups. The time to discharge was similar between the groups.
Conclusions Propofol was associated with a better recovery profile and neurological condition than isoflurane, as indicated by shorter extubation and OR discharge times and better postoperative consciousness.

Keywords Isoflurane · Propofol · Craniotomy · Emergence · Consciousness

Y. Miura (✉) · K. Kanazawa
Department of Dental Anesthesiology, Health Sciences University of Hokkaido, Tobetsu-cho, Ishikari-gun, Hokkaido 061-0293, Japan
e-mail: ymiura@hoku-iryo-u.ac.jp

K. Kamiya
Division of Anesthesiology, Yamagata Prefectural Central Hospital, Yamagata, Yamagata, Japan

M. Okada · M. Nakane · A. Kumasaka · K. Kawamae
Department of Anesthesiology, Yamagata University School of Medicine, Yamagata, Yamagata 990-2292, Japan

Introduction

In major intracranial surgeries for space-occupying lesions, anesthesiologists have long sought the anesthetic regimen which provides rapid emergence with clearer consciousness that would allow immediate neurological assessment for possible surgical complications. Isoflurane was formerly considered to be appropriate anesthetic due to its robust suppression of cerebral metabolism [1]; however, more recently, propofol- or sevoflurane-based anesthetic regimens are primarily adopted in the neuroanesthesia context [2–4]. These three anesthetics satisfy the requirements of good neuroanesthesia [5]: hemodynamic stability and avoidance of increases in intracranial pressure. In contrast, each of these three agents has a different pharmacology and mechanism of action and, therefore, it is likely that the emergence state is influenced by the choice of anesthetic used. Sevoflurane has been shown to provide faster emergence than isoflurane [6], while being similar to

propofol when administered for maintenance of anesthesia [7]. However, studies on the recovery profile of propofol in comparison with isoflurane have shown inconsistent results, variously including a faster return of normal orientation [8], a tendency to slower recovery [9], and similar emergence times [10].

At Yamagata University Hospital, all craniotomies for the resection of brain tumors carried out between 2000 and 2005 were exclusively performed or supervised by a single neurosurgeon. Only the anesthesia regimen was changed during this period: isoflurane had been the anesthesia of choice until May 2003, with a gradual switch to a propofol-based regimen thereafter. This change was made in accordance with the surgical team's demand. Intraoperative electrophysiological monitoring had been performed under isoflurane anesthesia; however, because of the interference on monitoring quality by isoflurane, avoidance of the agent was requested [11]. Given the uniformity of the surgical management at our hospital during the period 2000–2005, we therefore considered that a retrospective investigation of the anesthesia database on these 4 years would provide valuable information on the anesthesia recovery profiles of isoflurane and propofol.

Patients and methods

This is a retrospective study using the departmental anesthesia database. The ethical committee of Yamagata University Hospital approved this study. Acquisition of informed consent from each patient was validated with confirmation of agreement for the use of anesthesia data for research purposes. Adult patients with primary brain tumors at both supratentorial and infratentorial regions who underwent craniotomies for tumor removal between January 2002 and May 2005 were included in this study. Exclusion criteria were age <18 years, emergency surgeries, and early post-operative death within 1 month. A diagnosis of metastatic brain tumor was excluded because of the small number of patients. Patients were classified into two groups—those who received an isoflurane-based anesthesia regimen (ISO group) and those who received a propofol-based anesthesia regimen (PROP group)—either with or without a combination of nitrous oxide, depending on the main anesthetic administered during maintenance of anesthesia. Patients who were anesthetized with mixture of volatile anesthetic and propofol, which was seen during the transitional period of anesthesia regimen change, were excluded.

The following parameters were extracted from the database and medical records: demographic data, American Society of Anesthesiology (ASA) physical status, preoperative level of consciousness, preoperative incidence of convulsions, type of brain tumors, surgical postures, surgical time, anesthesia time, combination of nitrous oxide, fentanyl dosage, lowest and highest body temperature during surgery, total infusion volume, mannitol dose, urine output, extubation time, operating room (OR) discharge time, consciousness at the end of anesthesia, postoperative level of consciousness from postoperative day (POD) 0 to POD 7, postoperative incidence of nausea or vomiting, postoperative incidence of convulsions, and the days to discharge. The brain tumors were classified as benign or malignant according to the postoperative pathological diagnoses. Conscious state at the end of anesthesia was scored on a scale of 1 to 4 according the description by the attending anesthesiologists [1, awoke spontaneously or by gentle touch, obeyed commands; 2, aroused by voice or light stimuli, obeyed commands; 3, aroused by moderate stimuli, did not obey commands but met extubation criteria; 4, did not open eyes and returned to intensive care unit (ICU) intubated]. Preoperative and postoperative levels of consciousness were scored using the Japan Coma Scale (JCS), assessed four times per day independently by ward nurses and neurosurgeons; the worst value was used for analysis. Because most patients returned to the ward in the evening, JCS scores at POD 0 represented one of two assessments. JCS scores were converted to single digits for statistical purposes (Table 1). When nausea, vomiting, or convulsions occurred within 24 h postoperatively with appropriate treatment, their incidences were recorded.

Routine perioperative management during the study period

Two anesthesiologists, a resident and an attending, were in charge of the anesthetic management of each case. An attending anesthesiologist performed the preoperative examination and obtained informed consent from the patient or one of the family members. On the morning of the surgery, patients were given their regular medications and 20 mg famotidine subcutaneously. No sedatives were subscribed as premedication. Patients entered the OR at 8:30 a.m. Standard monitors were applied and radial arterial catheter was established, then oxygen administration was started. In ISO, anesthesia was induced with thiopental 3–5 mg/kg followed by atropine 0.5 mg and fentanyl 2–4 μg/kg, following which isoflurane inhalation was instituted. The isoflurane concentration during maintenance of anesthesia was left to the discretion of the attending anesthesiologist, although the dose was adjusted to maintain the end tidal isoflurane concentration at or above 1 %, as is departmental policy. In the PROP group, anesthesia was induced with propofol 1.5–2.0 mg/kg followed by atropine 0.5 mg and fentanyl 2–4 μg/kg. A bispectral (BIS) sensor was applied either to the occipital or forehead

Table 1 Japan Coma Scale for grading impaired consciousness and its conversion to single digits for statistical analyses

Japan Coma Scale		Single digit conversion
One-digit code		
Score	Description: the patient is awake without any stimuli, and is	
0	Completely conscious	0
1	Almost completely conscious	1
2	Disoriented in time, place and person	2
3	Unable to recall name and date of birth	3
Two-digit code		
Score	Description: the patient can be aroused	
10	Easily by being spoken to (responsive with purposeful movements, phrases or words)[a]	4
20	With loud voice or shaking the shoulders (almost steadily responsive with very simple words-yes or no, or movements)[a]	5
30	Only by repeated mechanical stimuli. The patient falls into the previous state on cessation of stimulation	6
Three-digit code		
Score	Description: the patient cannot be aroused by any forceful mechanical noxious stimuli, and	
100	Responds with movements to avoid the stimulus	7
200	Responds with slight movements including decerebrate and decorticate postures	8
300	Does not respond at all except for change in respiratory rhythm	9

[a] Used in patients who cannot open their eyes for any reason

region, depending on the surgical position [12], and either isoflurane or propofol dosage was adjusted to maintain intraoperative BIS values at between 30 and 50. In both groups, fentanyl and nitrous oxide were the only analgesics administered. The dosage of fentanyl or use of nitrous oxide was left to the discretion of the attending anesthesiologist. Vecuronium, which was used to facilitate intubation and was administered intermittently during surgery, was reversed when electrophysiological monitoring was planned. During the monitoring, fentanyl was administered as a bolus when movement or bucking events were anticipated. All surgeries were performed with the patient in either the supine or prone position, depending on the surgical requirement. The trachea was intubated orally for surgery with the patient in the supine position and nasally for surgery in the prone position. Patients were wrapped with a warming cover, targeting a core temperature (bladder temperature) of 36–37 °C with the aid of a temperature management unit (Bair Hugger®, Eden Prairie, MN). A local anesthetic, i.e., 1 % lidocaine with epinephrine 1:200,000, was infiltrated at the sites of head pin fixation and the scalp over the surgical field. Mannitol, 300 ml, was routinely infused when the scalp incision was started, with more being administered when requested by the surgeon. Lactated ringer solution, 3–4 ml/kg/h, was infused as a maintenance fluid, and hydroxyethyl starch or packed red cells were infused when necessary. Ventilation and the inspired oxygen fraction (F_IO_2) were adjusted to achieve slight hypocapnia or normocapnia and to maintain the P/F ratio at >350. Normotension, with a mean arterial pressure (MAP) >60 mmHg, was targeted, and ephedrine or dopamine were administered as needed. Hypertension, defined as a systolic blood pressure >140 mmHg, was treated with nicardipine or prostaglandin E_1. If needed, insulin was used to maintain blood glucose at <150 mg/dl. After the tumor was removed, an infusion of 250 mg of phenytoin was given.

At the end of the surgery, before subcutaneous suturing, the local anesthetic was re-infiltrated into the scalp. Isoflurane or propofol administration was terminated without tapering of the dose when the patient position was secured after detachment from the Mayfield head holder. Residual muscle relaxation was reversed. Patients were extubated when minute ventilation and airway reflexes had recovered sufficiently. The patients were observed on the surgical table and after confirmation of the patients' respiratory and hemodynamic stability, the attending anesthesiologist gave permission for the patient to be moved out of the OR.

Statistical analysis

Data are presented as mean ± standard deviation (SD) for continuous variables. Categorical variables are shown as number of patients and percentages. Perioperative JCS distribution is expressed using box plots. Student's *t* test was used to compare continuous variables between groups. Categorical variables were compared using the chi-square test or Fisher's exact test as appropriate. Friedman's test was used to analyze perioperative changes of JCS scores and to perform multiple comparisons within a group. In our study,

both isoflurane and propofol were not stratified according to nitrous oxide use or fentanyl dosage. However, as both anesthetics might influence outcome, the effects of nitrous oxide combination and fentanyl dosage on outcome variables were analyzed in separate groups using Pearson's product moment correlations for continuous variables and Spearman's rank correlations for categorical variables. Analyses were performed using JMP ver. 6.0.3 software (SAS Institute, Cary, NC). The statistical script to perform Friedman's test was provided by the company. $P < 0.05$ was considered to indicate statistical significance.

Results

Demographic and intraoperative variables

During the 4-year study period 202 elective craniotomies for the removal of brain tumors were conducted. Of these 202 patients, 42 were excluded from the analyses: 30 patients due to the use of a mixture of anesthetics, eight patients due to diagnoses of metastatic brain tumors, and five patients due to imperfect postoperative JCS recordings. Hence, 159 patients were ultimately included in the study, 77 in the ISO group and 82 in the PROP group.

Table 2 shows the demographic data and intraoperative variables of the patients. Patients in the two groups were comparable in terms of age, sex, body mass index, preoperative JCS score, incidence of preoperative convulsions, ratio of the two surgical postures, ratio of benign and malignant tumors, and surgical and anesthesia time. The preoperative general condition was significantly worse among patients in the PROP group, as indicated by ASA physical status. Mean total dosages of isoflurane and propofol were 134 ± 56 and 3,850 ± 1627 mg, respectively. The use of nitrous oxide and fentanyl in combination with the primary anesthetic was significantly more common in patients of the PROP group. Infusion volumes and

Table 2 Group demographics and intraoperative variables

Variables	ISO ($n = 77$)	PROP ($n = 82$)	P value
Age (years)	49.7 ± 17.4	48.5 ± 17.6	0.6657
Gender (female)	42 (54.6)	51 (62.2)	0.3393
Body mass index (kg/m^2)	23.5 ± 3.1	23.9 ± 3.9	0.4396
ASA physical status			
1	34 (44.2)	20 (24.7)	0.0255*
2	43 (55.8)	60 (74.1)	
3	0 (0)	1 (1.2)	
Preoperative JCS score			
0	70 (90.9)	64 (78.1)	0.1718
1	3 (3.9)	8 (9.8)	
2	3 (3.9)	6 (7.3)	
3	0 (0)	3 (3.7)	
4	1 (1.3)	1 (1.2)	
Preoperative convulsions	52 (67.5)	51 (62.2)	0.5100
Types of brain tumor			
Benign	47 (61.0)	43 (52.4)	0.3370
Malignant	30 (39.0)	39 (47.6)	
Surgical posture (supine:prone)	53:24	52:30	0.5059
Isoflurane dose (ml)	134 ± 56	0	–
Propofol dose (mg)	0	3,850 ± 1,627	–
Combination with nitrous oxide	16 (20.8)	44 (53.7)	<0.0001*
Fentanyl dose (μg)	434 ± 118	605 ± 197	<0.0001*
Infusion volume (ml/kg/h)	5.13 ± 1.37	5.46 ± 1.51	0.1575
Mannitol dose (g/kg)	1.13 ± 0.35	1.08 ± 0.36	0.3579
Urine output (ml/kg/h)	2.74 ± 1.04	3.38 ± 1.40	0.0020*
Lowest body temperature (°C)	36.1 ± 0.50	35.8 ± 0.48	<0.0001*
Highest body temperature (°C)	37.5 ± 0.71	37.0 ± 0.66	<0.0001*
Surgical time (min)	454 ± 141	497 ± 157	0.0739
Anesthesia time (min)	606 ± 147	635 ± 155	0.2213

Values are presented as the mean ± standard deviation (SD) for continuous variables and as the number of patients and percentages (in parenthesis) for categorical variables

ISO Isoflurane-based anesthesia regimen, *PROP* propofol-based anesthesia regimen, *ASA* American Society of Anesthesiologists, *JCS* Japan Coma Scale

* Statistically significant difference ($P < 0.05$) between groups

mannitol doses were not significantly different between the groups, although urine output was significantly higher in the PROP group patients. It was also noted that both the lowest and highest values of intraoperative body temperature were significantly lower in PROP group patients.

Anesthesia recovery profiles and postoperative outcomes

Table 3 summarizes the anesthesia recovery profiles and postoperative outcomes of the patients. PROP group patients had significantly shorter extubation times and OR discharge times than ISO group patients. Shivering was present in 6 and 13 % of patients in the ISO and PROP groups, respectively. Overall conscious state at OR discharge was significantly improved in PROP group patients. Of the four patients who could not be extubated before transfer to the ICU, one belonged to the ISO group and three to the PROP group; these patients' preoperative JCS scores were classified as 3 or 4. Perioperative JCS changes are shown in Fig. 1. In the ISO group, significantly higher JCS scores lasted until POD 2 as compared to their preoperative values, whereas in the PROP group, JCS scores on POD 2 were not significantly different from their preoperative values. JCS scores on POD 0 were significantly higher in the ISO group compared to the PROP group. Other variables, such as incidence of nausea or vomiting, convulsions, and days to discharge, were similar between the two groups. There were no statistically significant correlations between either nitrous oxide combination and fentanyl dosage on any outcome variables.

Table 3 Anesthesia recovery profiles and postoperative outcomes

Variables	ISO ($n = 77$)	PROP ($n = 82$)	P value
Extubation time (min)	39.6 ± 14.6	29.5 ± 14.1	<0.0001*
OR discharge time (min)	67.2 ± 18.0	54.2 ± 17.5	<0.0001*
Incidence of shivering	6 (7.8)	13 (15.9)	0.1451
Consciousness level at OR discharge			
1	4 (5.2)	29 (35.4)	<0.0001*
2	48 (62.3)	41 (50.0)	
3	24 (31.1)	9 (10.9)	
4	1 (1.3)	3 (3.7)	
Postoperative nausea and vomiting	23 (33.8)	21 (26.6)	0.3703
Postoperative convulsions	6 (7.9)	8 (9.8)	0.7830
Days to discharge (day)	42 ± 36	42 ± 33	0.9809

Values are presented as the mean ± SD for continuous variables and number of patients and percentages for categorical variables

OR operating room

* Statistically significant difference ($P < 0.05$) between groups

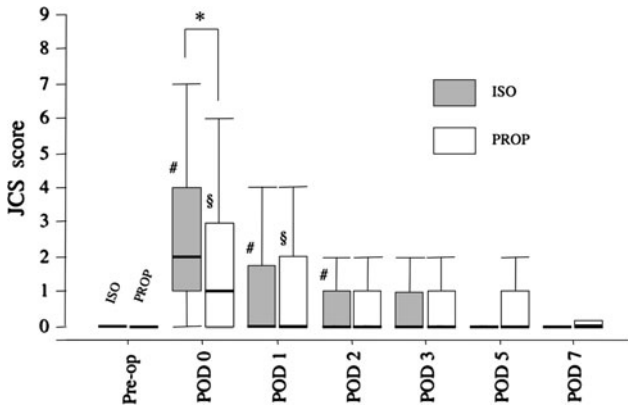

Fig. 1 Perioperative changes in Japan Coma Scale (JCS) scores. Data are depicted using a *box plot*. *ISO* Isoflurane-based anesthesia regimen, *PROP* propofol-based anesthesia regimen, *Pre-op* preoperative, *POD* postoperative day. *Thick line* indicates median value. #Significantly different from Pre-op values in the ISO group, §significantly different from Pre-op values in the PROP group, *significantly different between groups

Discussion

We conducted this retrospective study to clarify the recovery profile of and postoperative neurological condition after isoflurane- and propofol-based anesthetic regimens in patients undergoing craniotomy for primary brain tumor removal. During our investigation of the medical records, in which intraoperative anesthetic depth was controlled to have a BIS value of 30–50 for both groups, we found that propofol-based anesthetic regimens promoted a faster recovery with a better postoperative neurological condition than isoflurane, as indicated by the shorter extubation times and earlier OR discharge, as well as by the better postoperative consciousness level. propofol-based regimens also resulted in a higher urine output and lower body temperature intraoperatively.

Anesthetics for neuroanesthesia should provide hemodynamic stability, maintain coupling between cerebral blood flow and metabolism, preserve cerebrovascular autoregulation, avoid increases in intracranial pressure, and promote rapid recovery [3, 4]. Modern anesthetics, regardless of their pharmacological classification, meet these requirements in patients with normal intracranial compliance to varying degrees [5]. However, the literature regarding the recovery profiles of isoflurane and propofol seem inconsistent. Extubation time is a commonly used index to measure the recovery profile. The extubation time for propofol-based regimens has been reported as 3.5 min with a continuous infusion of fentanyl (anesthesia time 333 ± 120 min) [10] and 18.3 ± 2.1 min in combination with remifentanil (anesthesia time 330 ± 98 min) [7]. For isoflurane, extubation times have been variously reported as: 2.1 min (median) with 2.8 ± 1.5 MAC-hour isoflurane

combined with 60 % nitrous oxide (anesthesia time 341 ± 94 min) [10], 4–5 min with supplemental isoflurane in a remifentanil- or fentanyl-based regimen (median duration of anesthesia time 298 and 294 min) [13], 4–5 min with a 0.55 % end-tidal isoflurane concentration (exposure time 322 ± 114 min) [9], and 30.0 ± 28.0 min with 0.7MAC isoflurane (exposure time 6.8 ± 1.8 h) [6]. Actually, extubation time appears to be related not to the anesthetic used or to the exposure time but to anesthetic management. Longer extubation times were observed when anesthetics were administered without tapering their dose until the removal of the Mayfield head holder [6, 7], as was done in the patients in this study. Hence, the results of our study and those of other studies seem to suggest that the different recovery profiles of isoflurane and propofol become manifest when the anesthetics are administered right up until the end of the surgical procedure without any tapering of their dose.

Along with the recovery profile, postoperative consciousness level is also critical in the assessment of the patient's neurological condition. Varying short-term neurological outcomes have been reported in prospective trials. Return of orientation and response to commands were variously faster in propofol–alfentanil-treated patients than in isoflurane-treated patients [8], tended to be slower with propofol than isoflurane [9], and was similar between propofol/fentanyl and fentanyl/nitrous oxide [10]. In the current investigation, the conscious state at OR discharge and JCS score at POD 0 were significantly improved in the PROP group as compared to the ISO group. We can only speculate on the reason for the different postoperative consciousness levels between the two groups. One explanation might be the protracted effect of delayed emergence observed in the ISO group, which likely had sustained effects on patient consciousness. It is also possible that the higher urine output in PROP group patients had some effect on cerebral edema formation. In a dog model of induced hypotension, a slightly lower renal blood flow was observed at various MAP levels under isoflurane as compared to propofol–alfentanil anesthesia [14]. Although induced hypotension was not performed in our patients, due to the prolonged duration of surgery, even small changes in renal blood flow might have resulted in significant effects.

Several limitations of this study, which are inherent to the retrospective study design, should be noted. Patients were not randomized and two anesthetic regimens were provided at separate periods. The outlines of the anesthetic management were standardized, except for anesthetic regimens; however, details were dependent on attending anesthesiologists, such as administration of fentanyl, combination of nitrous oxide, timing of extubation and OR discharge, and the assessment of postanesthesia conscious state. In particular, the fentanyl dose and combined ratio of nitrous oxide were significantly different between groups. Although, post hoc analysis revealed insignificant effects of these agents on outcome variables, differences in analgesics use still remain major confounding factors.

In summary, in patients undergoing craniotomy for removal of primary brain tumors, propofol improved short-term outcomes, as indicated by a better recovery profile and better postoperative consciousness levels, as compared to isoflurane. Both isoflurane and propofol did not affect postoperative outcome variables, such as incidence of nausea and vomiting, incidence of convulsion, and days to discharge. Higher intraoperative urine output and lower body temperatures were also seen in the PROP group patients. Although retrospective in nature, our findings suggest that the quality of neuroanesthesia is influenced by the choice of anesthetic agents.

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Conflicts of interest Authors have no conflict of interest.

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