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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,

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 ≥ 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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