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.

Acknowledgments This study was funded by Grants-in-Aid for Research on Policy Planning and Evaluation (Grant Number: H19-Policy-001) from the Ministry of Health, Labour and Welfare, Japan.

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British Journal of Anaesthesia **106** (2): 202–7 (2011)
Advance Access publication 8 December 2010 · doi:10.1093/bja/aeq359

BJA

NEUROSCIENCES AND NEUROANAESTHESIA

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

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Editor's key points

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

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

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

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

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

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

Accepted for publication: 19 October 2010

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

Methods

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

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

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

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

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

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

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

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

Data analysis

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

Results

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

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

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

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

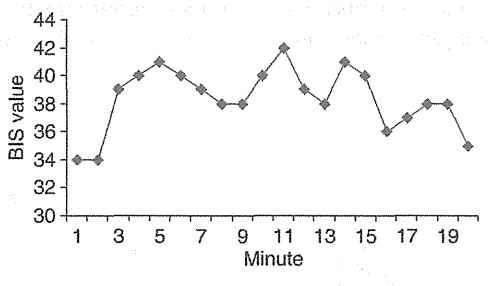

Fig 1 BIS values of one representative patient during 1–20 min after the effect-site concentration of propofol reached and remained 3.0 μg ml^{-1}.

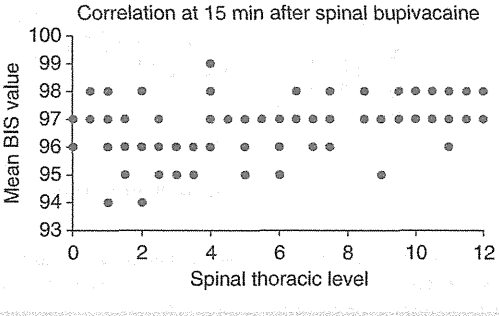

Fig 2 Scattergram showing the relationship between the spinal thoracic level of spinal sensory blockade and BIS values at 15 min after the spinal administration of bupivacaine. The correlation coefficient for this time was 0.135 (P=0.195). Spinal anaesthesia itself did not cause any significant decreases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

anaesthesia itself did not cause any significant decreases in BIS values at 15 min after spinal anaesthesia.

The relationship between spinal thoracic levels of sensory block and BIS values after propofol administration is illustrated in Figure 3A–D. The correlation coefficients between spinal thoracic levels at 15 min after spinal anaesthesia and BIS values were 0.800, 0.848, 0.804, and 0.801, respectively, between 1 and 5, 6 and 10, 11 and 15, and 16 and 20 min after the estimated effect-site concentration of propofol attained a constant level of 3.0 μg ml^{-1} ($P<0.001$ for each value).

Discussion

The present study demonstrates that BIS significantly correlates with the spread of spinal sensory block under conditions of identical predicted effect-site concentration of propofol. We conducted this study under deep sedation because the BIS value may be affected by arousal, movement, cough, or noise under light or no sedation.[7 8] Our results suggest that depth of sedation with propofol is influenced by the height of the spinal sensory block at 15 min after spinal anaesthesia.

The proposed mechanisms of the sedative effects induced by spinal anaesthesia include systemic general anaesthetic effects of absorbed local anaesthetics, rostral spread of the local anaesthetics through cerebrospinal fluid with direct actions on the brain, and decreased facilitatory sensory input to the reticular activating system due to loss of proprioceptive inputs from skin, muscles, or joints.[1 13 14] However, no previous studies have demonstrated that the sedative effect is due to the spread of spinal anaesthesia or to the dose of intrathecally administered local anaesthetics. The present study revealed that the local anaesthetics delivered to the brain after systemic absorption into the circulation is not the only cause of the decrease in BIS values because the dose of bupivacaine was identical in all patients in this study. The depth of sedation induced by spinal anaesthesia depends on the extent of spinal sensory block.

There are several studies examining the effects of the different levels of spinal anaesthesia on BIS values in patients with light to no sedation.[2 5 6] Our results are consistent with these studies,[2 5 6] suggesting that a higher spinal anaesthesia deepens the level of depth of sedation, mirrored by the BIS, compared with a lower spinal anaesthesia. However, in these previous studies, the differential spread of spinal anaesthesia was produced by different doses or baricity of the local anaesthetic. Our study demonstrated that the sedative effect of spinal block produced by equal dose of the same anaesthetic was dependent on the level

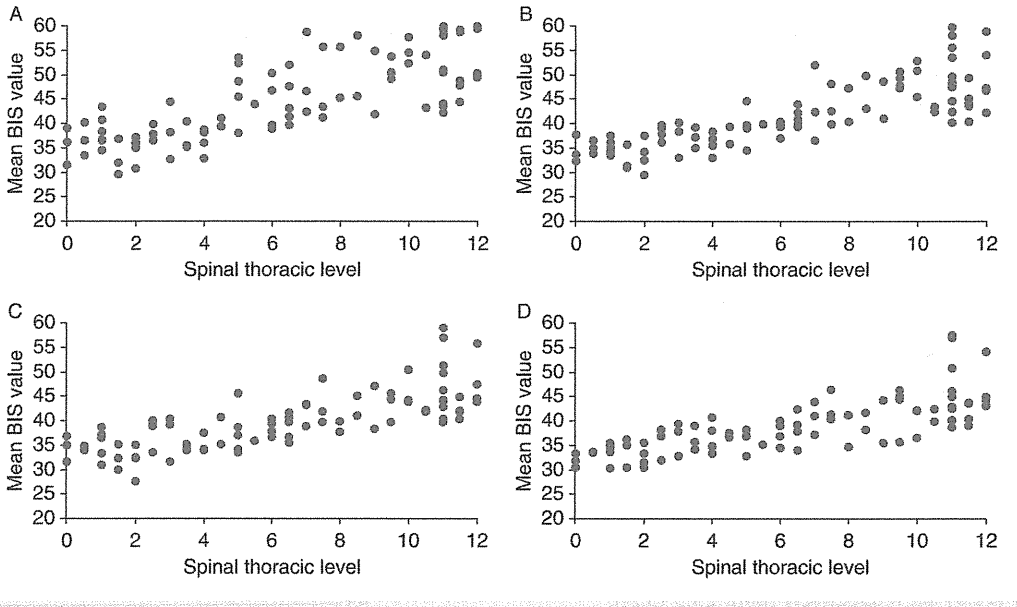

Fig 3 Scattergram showing the relationship between spinal thoracic level of spinal sensory blockade at 15 min after spinal anaesthesia and BIS values during the periods between 1 and 5 min (A), 6 and 10 min (B), 11 and 15 min (C), and 16 and 20 min (D) after the effect-site concentration attained a constant level of 3.0 μg ml^{-1}. The points represent the mean values calculated from data for the 5 min interval for individual patients. The vertical axis represents BIS values. The horizontal axis represents the spinal thoracic level in which 0.0, 1.0, and 2.0 correspond to C8, Th1, and Th2, respectively. The spinal levels are the mean values of the right and left spinal thoracic levels; therefore, the spinal levels are represented as 0.0, 0.5, 1.0, 1.5, 2.0, and so on. The correlation coefficients between spinal levels and BIS values were 0.800, 0.848, 0.804, and 0.801, respectively, at 1–5, 6–10, 11–15, and 16–20 min after the effect-site concentration of propofol reached and remained at 3.0 μg ml^{-1}. The regression coefficients on each linear regression line were 1.7074, 1.3977, 1.1284, and 1.0270, respectively, at 1–5, 6–10, 11–15, and 16–20 min.

of spinal sensory block at 15 min after spinal anaesthesia when the estimated effect-site concentration of propofol remained at 3.0 μg ml^{-1}. In contrast to our findings, Toprak and colleagues[15] reported that the requirements of sedatives were decreased by spinal anaesthesia, although this decrease did not significantly correlate with the level of the spinal sensory block. In Toprak and colleagues' study, spinal anaesthesia was administered with 10 and 17.5 mg of hyperbaric bupivacaine and the obtained mean anaesthetic levels were close to each other, at Th7 and Th9, in the two groups compared.[15] The proximity of the spinal levels could explain the difference between their results and ours. From their study, it appears that it is the dose of spinally administered local anaesthetics that affects the sedative effect induced by spinal anaesthesia. Conversely, the present study revealed that the sedative effect, mirrored by BIS values, is dependent on the height of spinal sensory block at 15 min after spinal anaesthesia, when the dose and baricity of the local anaesthetic for spinal anaesthesia remain unchanged.

The spinal thoracic level did not significantly correlate with BIS values before sedation at 15 min after spinal anaesthesia in our study. It has been reported that spinal anaesthesia alone leads to a significant decrease in BIS values in patients and healthy volunteers.[2–4] In Pollock and colleagues'[4] study, the volunteers were placed in a darkened room with soft music to measure BIS values before and after spinal anaesthesia. In contrast, our patients were undergoing surgery in a well-lit operating theatre, were free to communicate with medical staff, and were spoken to by the anaesthetist to assess the height of spinal block every minute, which would have repeatedly stimulated the patients. It is possible that those stimuli may have counteracted the sedative effects of spinal anaesthesia before the induction of general anaesthesia in our study. Furthermore, it was reported that the sedative effect induced by spinal anaesthesia starts to appear at 15 or 20 min after spinal anaesthesia.[3 5] Thus, evaluation of the effect of spinal anaesthesia on the depth of sedation at 15 min after spinal anaesthesia might have been too early. These two factors might explain why there was no correlation between BIS values and the level of spinal anaesthesia at 15 min after spinal anaesthesia.

There are a few limitations to the present study. First, the attending anaesthetist was not blinded to the study; however, the level of spinal anaesthesia was determined before data collection and analysis. The bias of the attending anaesthetist could not have affected the BIS values because the data collection was automatically made from the monitor recording system. Secondly, 15 min may not be long enough for the local anaesthetic to cease its maximal rostral spread after spinal anaesthesia. Hence, the spinal level at 15 min post-spinal administration is not likely to be the same as that during the later periods after propofol administration. In our study, correlation was evaluated between the spinal level at 15 min after spinal administration and BIS values during the fixed time periods after patients were sedated with propofol. However, according to our study protocol, the time period from administration of spinal anaesthesia to setting up the concentration of TCI was approximately equal in all the patients. The consumption of propofol from the induction of anaesthesia to the periods evaluated was also approximately equal among patients, when adjusted for body weight. Therefore, the calculated BIS value during each period can be evaluated for comparison with the spinal sensory level at 15 min after spinal administration.

The present study demonstrated that BIS values significantly correlate with the level of spinal block assessed at 15 min after spinal anaesthesia under deep sedation with propofol in young and middle-aged patients. The depth of sedation induced by spinal anaesthesia is influenced by the spread of spinal sensory block.

Conflict of interest

None declared.

Funding

This study was supported by departmental and institutional funding only.

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British Journal of Anaesthesia **106** (6): 823–6 (2011)
Advance Access publication 29 April 2011 · doi:10.1093/bja/aer098

BJA

Reversibility of rocuronium-induced profound neuromuscular block with sugammadex in younger and older patients

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Editor's key points

- The efficacy of sugammadex in older patients has not been defined.
- Reversal of profound rocuronium block (PTC 2) was compared in older and younger patients.
- Full recovery was achieved with sugammadex in all patients but was slower in the older ones.
- Age-related cardiovascular changes are a possible explanation.

Background. This study compared the reversibility of rocuronium-induced profound neuromuscular block with sugammadex in younger and older patients.

Methods. Fifteen younger (20–50 yr) and 15 older (≥70 yr) patients were sequentially enrolled in this study. After induction of anaesthesia and laryngeal mask insertion, contraction of the adductor pollicis muscle in response to ulnar nerve stimulation was quantified using acceleromyography during 1.0–1.5% end-tidal sevoflurane and remifentanil anaesthesia. All patients initially received rocuronium 1 mg kg^{-1}, followed by 0.02 mg kg^{-1} when a post-tetanic count (PTC) of 1 or 2 was observed. After completion of surgery, at reappearance of 1–2 PTC, the time required for a single bolus dose of 4 mg kg^{-1} sugammadex to produce recovery to a train-of-four (TOF) ratio of 0.9 was recorded.

Results. There were no differences in the total dose of rocuronium administered between the younger [mean (SD): 93.4 (17.5) mg] and the older [97.5 (32.2) mg] groups. In all patients, adequate recovery of the TOF ratio to 0.9 was achieved after administration of sugammadex, although it was significantly slower in the older [3.6 (0.7) min, $P<0.0001$] than in the younger group [1.3 (0.3) min]. There were no clinical events attributable to recurarization.

Conclusions. Sugammadex can adequately restore neuromuscular function in older patients, although a longer time is required to recover from profound rocuronium-induced neuromuscular block than in younger patients.

Keywords: age factors; monitoring, neuromuscular function; neuromuscular block, antagonism; neuromuscular block, rocuronium; sugammadex

Accepted for publication: 10 March 2011

Traditionally, anticholinesterases have been used to antagonize residual non-depolarizing neuromuscular block. However, they have limited efficacy in adequately reversing profound neuromuscular block induced by neuromuscular blocking agents with an intermediate duration of action.[1–5] For example, the time from administration of rocuronium 0.45 mg kg^{-1} to recovery of the train-of-four (TOF) ratio to 0.9 could not be significantly shortened by the maximum dose of neostigmine 0.07 mg kg^{-1} given 5 min after rocuronium (mean value: 42.1 min) in adult patients when compared with the time for spontaneous recovery (54.3 min).[1] It is therefore recommended that antagonism with neostigmine should be delayed until at least the second twitch of the TOF response is detectable to completely restore neuromuscular function.[6] Even in these circumstances, it takes up to 10 min to achieve the full effect of anticholinesterases.[7] In comparison, sugammadex, a modified gamma cyclodextrin, is a selective relaxant binding agent specifically designed to encapsulate rocuronium,[8] which can, therefore, promptly restore neuromuscular function regardless of any levels of neuromuscular block as the dose is increased.[9–11] If the marked reductions in recovery time are replicated in routine clinical practice, sugammadex contributes to save time and has the potential to be cost-effective compared with neostigmine.[12] Chemically encapsulating the rocuronium molecule with sugammadex results in a rapid decrease in plasma concentration of free rocuronium and induces rocuronium molecules to extensively diffuse from the neuromuscular junction into plasma along the concentration gradient of free rocuronium.[13] Therefore, in older patients with a low cardiac output[14] and regional blood flow,[15] a slower increase in the plasma concentration of sugammadex and a slower facilitated recovery by sugammadex would be expected, when compared with younger adults. However, the age-related change in the efficacy of sugammadex has not been completely investigated. The only study[16] carried out in elderly patients showed a slower recovery from the time of reappearance of the second twitch in the TOF to a TOF ratio of 0.9 following sugammadex 2 mg kg^{-1} with increasing patient age. The average time of 3.6 min required

to attain a TOF ratio of 0.9 in patients aged ≥75 yr is significantly longer when compared with the 2.3 min in younger adults aged 18–64 yr. The efficacy of sugammadex in the reversal of deep neuromuscular block in the elderly has not been examined. Therefore, the aim of this study was to compare the reversibility of profound rocuronium-induced neuromuscular block, quantified by a mode of the post-tetanic counts (PTCs), with sugammadex between younger and older patients.

Methods

After approval of the protocol by the Hospital Ethics Committee on Human Rights in Research, 30 adult female patients consented to participate in this study. Patients were ASA physical status I–III, aged between 20 and 50 yr (younger) or ≥70 yr (older), and undergoing elective gynaecological surgery under general anaesthesia. None of the patients had neuromuscular, hepatic, or renal disorders, or were taking any drug known to interact with neuromuscular blocking agents. Patients whose BMI was ≥25 or <18.5 were excluded from the study. Premedication consisted of ranitidine 150 mg administered orally before going to bed on the day before surgery and on the morning of surgery. On arrival at the operating theatre, all patients were monitored with ECG, non-invasive arterial pressure, and pulse oximetry. Ringer's solution (8–10 ml kg^{-1} h^{-1}) was given i.v. in the right forearm. Patients were sequentially enrolled into the study groups on the basis of their age; each group comprised 15 patients. The neuromuscular block was monitored at the adductor pollicis muscle. General anaesthesia was induced with fentanyl 2–4 μg kg^{-1} and propofol 2.5 mg kg^{-1} i.v. while patients received 100% oxygen through an anaesthesia facemask. After loss of consciousness, a laryngeal mask was inserted without the aid of neuromuscular blocking agents. Anaesthesia was maintained with sevoflurane 1.0–1.5% end-tidal and remifentanil 0.2–0.3 μg kg^{-1} min^{-1}. Ventilation was adjusted to maintain end-tidal carbon dioxide between 4.3 and 5.1 kPa using a Multigas Unit AG-920R™ (Nihon Kohden, Tokyo, Japan). The rectal temperature of the patients was monitored using a Mon-a-Therm™ (Mallinckrodt, Anesthesia Products Inc., St Louis, MO, USA) and was maintained at >36°C using a warming mattress blanket (Thermacare™ and Medi-Therm II™, Gaymer Industries, Inc., NY, USA) and warmed i.v. fluids. Skin temperature over the adductor pollicis muscle was recorded every 15 s throughout the experiment using a surface probe in the acceleromyograph and maintained at >32°C. After a stable depth of anaesthesia was obtained, the ulnar nerve at the wrist was stimulated supramaximally with square-wave stimuli of 0.2 ms duration, which were delivered in a TOF mode at 2 Hz every 15 s. Contraction of the ipsilateral adductor pollicis was measured using an acceleromyograph (TOF-Watch SX™, Organon Ltd, Dublin, Ireland). All data were collected on a computer and monitored throughout the study. After the control TOF, stimuli were administered for a minimum of 10 min to stabilize the TOF responses.[17] Then, all patients received rocuronium 1 mg kg^{-1} i.v. The ulnar nerve was repeatedly stimulated in a TOF mode at 2 Hz every 15 s. A PTC mode was initially applied 5 min after obtaining complete neuromuscular block and repeated every 6 min.[18] Whenever 1 or 2 PTCs were observed, rocuronium 0.02 mg kg^{-1} was given until the end of the surgical procedure. All patients received sugammadex 4 mg kg^{-1} when a PTC of 1–2 was present after the last dose of rocuronium, and the time required for facilitated recovery to a TOF ratio of 0.9 was recorded. The TOF ratio of 0.9 normalized by the baseline TOF ratio was monitored.[17 19] Sevoflurane and remifentanil were continued during recovery from neuromuscular block. Patients were monitored for postoperative respiratory events, such as respiratory distress and decrease in Sp_{O_2}, caused by recurarization, for 24 h after operation.

The sample size was calculated based on previous data on the averaged recovery time from profound rocuronium-induced neuromuscular block to a TOF ratio of 0.9, facilitated by sugammadex 4 mg kg^{-1} in younger adult patients [1.7 (0.7) min].[20] We considered a 50% increase (2.55 min) in the recovery time to be clinically relevant. To obtain statistically significant results with α=0.05 and a power of 0.80 required 12 patients in each group. To compensate for any dropouts, we enrolled 15 patients in each group. Data are presented as mean (SD) and (range). Statistical analysis was performed using the StatView™ software for Windows (SAS Institute, Cary, NC, USA). The unpaired Student's *t*-test was used for comparing data between the two groups. A *P*-value of <0.05 was considered statistically significant.

Results

Data from all the 30 patients could be included in the analyses. The mean age in the younger patients was 38.4 (3.5) yr and 75.9 (6.1) for the older group (Table 1). The duration of anaesthesia was significantly longer in older [177.5 (45.7) min, *P*=0.0015] than in the younger patients [118.5 (32.8) min]. However, the total dose of rocuronium given did not differ between the older [97.5 (32.2) mg] and the younger groups [93.4 (17.5) mg]. In all the patients, sugammadex was given at a PTC of 1–2. The time for facilitated recovery to a TOF ratio of 0.9 was significantly longer in the older [3.6 (0.7) (2.4–4.5) s, *P*<0.0001] than in the younger adults group [1.3 (0.3) (0.8–2.0) s]. There were no clinical events attributable to recurarization with rocuronium after operation.

Table 1 Patient characteristics. Data are presented as mean (SD) (range).

Monitoring muscle	Younger adult	Elderly
Age (yr)	38.4 (3.5) (32–46)	75.9 (6.1) (70–91)
Weight (kg)	57.2 (4.0)	55.9 (8.6)
Height (cm)	164.0 (7.5)	156.0 (10.0)

Discussion

This study shows that the speed of facilitated recovery from profound rocuronium-induced neuromuscular block with sugammadex 4 mg kg^{-1} is age-related. The total recovery time to a TOF ratio of 0.9 in older patients is approximately three-fold longer than that in younger adults (3.6 *vs* 1.3 min). Although sugammadex is extremely useful to restore neuromuscular function even from profound rocuronium-induced neuromuscular block irrespective of age when compared with neostigmine, caution is recommended when using sugammadex, even with neuromuscular monitoring, especially in older patients.

Our results show that, even in older patients, reversal with sugammadex does not have to be delayed until the second twitch of the TOF response or spontaneous respiration is detectable, as is required with neostigmine. This indicates that a profound depth of neuromuscular block can be maintained during anaesthesia right up to the end of the surgery. For some thoracic and abdominal surgery, PTC stimulation is used to maintain a sufficient depth of neuromuscular block. A PTC level of at least 5 is required to achieve total diaphragmatic paralysis in response to tracheal suction.[21] So far, PTC stimulation has been clinically used to estimate the approximate interval to reappearance of the first twitch in response to TOF stimulation during intense neuromuscular block.[22] However, the rapid reversal effects of sugammadex are changing the use of PTC for maintaining deep neuromuscular block during clinical anaesthesia. The present study could contribute to this by demonstrating the safety and effectiveness of reversing a deep rocuronium-induced neuromuscular block with sugammadex.

Our study does not elucidate why complete recovery from an intense rocuronium-induced neuromuscular block after administration of sugammadex is slower in older patients. However, the onset of action of sugammadex injected is likely to be dependent on cardiac output and muscle blood flow. Especially in females, cardiac output decreases modestly with an age-related decline in heart rate.[14] Limb blood flow decreases progressively with advancing age, even in healthy men.[15] This lower blood flow may be explained by age-related reduced vascular conductance, the loss of muscle volume, and decline in oxygen consumption. Age-associated arteriosclerosis also contributes to further decrease in peripheral perfusion. A lower regional blood flow would result in a slower increase in the plasma concentration of sugammadex and a slower decrease in the plasma concentration of free rocuronium. Hence, free rocuronium molecules cannot rapidly diffuse from the neuromuscular junction into the plasma. Therefore, it seems reasonable that an age-related reduction in cardiac output and muscle blood flow is a primary cause of the slower recovery of neuromuscular function after sugammadex.

Volatile anaesthetics cause marked peripheral vasodilation. If simultaneously, arterial pressure can be maintained and cardiac output can be increased, a greater blood flow to the peripheral tissues will be expected during inhalation anaesthesia. This was verified in younger patients. When receiving 0.8–1.2% isoflurane in combination with 66% nitrous oxide, muscle blood flow in the forearm progressively increased in patients 18–34 yr of age. In contrast, forearm blood flow in patients 60–79 yr of age significantly decreased when compared with baseline values during isoflurane anaesthesia.[23] Although sevoflurane, as was used in our study, has quite similar cardiovascular actions to isoflurane, sevoflurane-induced reduction of left ventricular function, such as end-diastolic volume, ejection fraction, and cardiac output, is much greater in magnitude when compared with isoflurane.[24] It can therefore be estimated that the peripheral blood flow might have typically decreased in the older patients in our study. These changes in blood flow to peripheral tissues produced by sevoflurane may have contributed to the age-related variation in the recovery with sugammadex from rocuronium-induced neuromuscular block.

We did not strictly fix the end-tidal concentration of sevoflurane to an age-adjusted minimum alveolar concentration (MAC) value and used a concentration of 1–1.5% according to routine clinical practice. This means that elderly patients may have received a greater MAC. Sevoflurane significantly enhances the effect of neuromuscular blocking agent[25] and therefore, the efficacy of sugammadex may theoretically be diminished during sevoflurane anaesthesia. However, sugammadex has been shown to be equally effective for reversal of rocuronium-induced neuromuscular block during sevoflurane or propofol anaesthesia.[26–28] It is therefore conceivable that sevoflurane does not pharmacodynamically inhibit chemical binding between rocuronium and sugammadex. In contrast, it remains possible that the difference in sevoflurane concentration between the two groups may affect the reduction in cardiac output and regional blood flow as mentioned above and consequently change actions of sugammadex in older patients. In addition, the longer duration of sevoflurane anaesthesia in the older patients may have contributed.

In conclusion, sugammadex can restore neuromuscular function in older patients. However, a longer time is required for recovery from profound rocuronium-induced neuromuscular block than in younger patients. Further studies are warranted to examine the effective dose of sugammadex required in older patients for more rapid reversal of neuromuscular block.

Conflict of interest

T.S. has received speaker fees from MSD Inc., JAPAN.

Funding

Departmental funding.

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J Anesth (2011) 25:200–204
DOI 10.1007/s00540-010-1086-z

ORIGINAL ARTICLE

A randomized trial to identify optimal precurarizing dose of rocuronium to avoid precurarization-induced neuromuscular block

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Received: 2 November 2010 / Accepted: 12 December 2010 / Published online: 12 January 2011

Abstract
Purpose The aim of this study was to examine the safe precurarizing dose of rocuronium required to avoid neuromuscular block after precurarization.
Methods Twenty-four female patients were randomly allocated into two groups of 12 patients each. General anesthesia was induced and maintained with remifentanil and propofol, and a laryngeal mask was inserted without the aid of a neuromuscular blocking agent. Patients were randomized to receive either 0.03 or 0.06 mg/kg rocuronium as a precurarizing dose. Neuromuscular block was monitored using acceleromyographic train-of-four (TOF) of the adductor pollicis muscle. Three minutes after the precurarization, all patients received suxamethonium 1.5 mg/kg and were graded on severity of fasciculations.
Results The average TOF ratio was kept above 0.9 even 3 min after precurarization with 0.03 mg/kg rocuronium. In contrast, in patients who received 0.06 mg/kg rocuronium, the ratios significantly decreased to 0.72 (0.14) [mean (SD), $P < 0.004$] and 0.68 (0.18) ($P < 0.006$) 2 min and 3 min after the precurarization, respectively. No visible muscle movement was observed following suxamethonium injection, except that one patient who received 0.03 mg/kg rocuronium showed very fine muscle movements of the fingertips.
Conclusion Rocuronium at 0.06 mg/kg is an overdose for precurarization. The results of the present study demonstrate that a safe and effective precurarizing dose of rocuronium is 0.03 mg/kg.

Keywords Precurarization · Rocuronium · Suxamethonium · Neuromuscular block

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Introduction

Many anesthetics can reduce lower and upper esophageal sphincter tone and tend to promote gastroesophageal regurgitation into the pharynx [1]. Therefore, rapid sequence intubation is frequently used to decrease the risk of pulmonary aspiration of gastric contents in a patient with a full stomach. Suxamethonium enables us to considerably shorten the interval from the patient's loss of consciousness following hypnotics to tracheal intubation and is considered to be appropriate for rapid sequence intubation [2, 3]. For such occasions, precurarization with a small dose of a nondepolarizing neuromuscular blocking agent has been widely used to prevent muscle fasciculation induced by suxamethonium and rise in intraabdominal pressure [3–6]. However, the technique may cause difficulty in breathing [7, 8], gastroesophageal regurgitation, and pulmonary aspiration associated with overdosage of precurarization [9]. The theoretical calculation using published pharmacodynamic and pharmacokinetic data showed that a dose of rocuronium equivalent to 10% of the ED_{95} (ED_{95} = 0.3 mg/kg) would rarely produce a measurable neuromuscular effect and should be therefore recommended as an appropriate dose for precurarization [10]. However, in previous studies [5, 11–13], 20–30% of the ED_{95} of rocuronium was generally used for precurarization, and effectiveness for defasciculation was examined. Although it is anticipated that a larger dose of rocuronium can greatly

suppress suxamethonium-induced fasciculation, the risk of a significant neuromuscular block in several minutes after the precurarization dosing may become greater. Unfortunately, the neuromuscular effect of precurarization has never been certified with any objective neuromuscular monitoring in clinical settings. Therefore, the main purpose of this study was to identify the optimal dose of rocuronium to avoid both neuromuscular block associated with precurarization and fasciculation induced by suxamethonium.

Materials and methods

After approval of the protocol by the Hospital Ethics Committee on Human Rights in Research, 24 adult female patients consented to participate in this study. Patients were ASA physical status I or II, 20–60 years of age, undergoing elective surgery. None of the patients had a difficult airway, previous history of hypertension, neuromuscular, hepatic, and renal disorders, or was taking any drug known to interact with neuromuscular blocking agents. Patients whose body mass index (BMI) was $\geq$25 or <18.5 were also excluded from the study. Premedication consisted of orally administered ranitidine 150 mg the night before and on the morning of surgery and i.m. midazolam 0.03–0.04 mg/kg. On arrival at the operating room, all patients were monitored with ECG, noninvasive blood pressure measurement, and pulse oximetry. An i.v. infusion of acetated Ringer's solution, 8–10 ml/kg/h, was started via the intravenous route. Anesthesia was induced with a continuous infusion of remifentanil at 0.5 μg/kg/min and a bolus of propofol 2 mg/kg. After confirming the bispectral index value of 60 or less (BIS monitor A-2000; Aspect Medical Systems, Norwood, MA, USA), a laryngeal mask was inserted without the aid of a neuromuscular blocking agent. Anesthesia was maintained with remifentanil 0.2 μg/kg/min and propofol 4–6 mg/kg/h. Ventilation was adjusted to maintain end-tidal carbon dioxide between 4.3 and 5.1 kPa using a Multigas Unit AG-920R (Nihon Kohden, Tokyo, Japan). Patient rectal temperature was monitored using a Mon-a-Therm (Mallinckrodt; Anesthesia Products, St. Louis, MO, USA) and was maintained at >36°C using a warming mattress and blanket (Thermacare and Medi-Therm II; Gaymer Industries, NY, USA) and warmed i.v. fluids. Skin temperature over the thenar muscle was recorded every 15 s throughout the experiment using a surface probe equipped in an acceleromyographic device and maintained at >32°C. After a stable depth of anesthesia was obtained, the unilateral ulnar nerve was stimulated at the wrist with supramaximal and square-wave stimuli of 0.2-ms duration, which was delivered in a train-of-four (TOF) mode at 2 Hz every 15 s. Contraction of the ipsilateral adductor pollicis was measured using an acceleromyograph (TOF-Watch SX; Organon, Dublin, Ireland). After the control TOF stimuli were administered for a minimum of 10 min to stabilize the responses [14], the T_1 value was readjusted to 100% and the patients received a precurarizing dose of rocuronium at either 0.03 or 0.06 mg/kg via computer-generated randomization. During a waiting time of 3 min, the time course of the TOF ratios was recorded. The TOF ratios were normalized by the baseline values [14]. Three minutes after the precurarizing dose, all patients received suxamethonium 1.5 mg/kg i.v. and were graded on severity of fasciculation using a four-point scale (0, no visible muscle movement; 1, very fine muscle movement of the face or the fingertips; 2, small fasciculations on the trunk and/or extremities; 3, strong fasciculations on the trunk and/or extremities) [12] by a staff anesthesiologist who was blinded to the grouping. Onset from the time of administration of suxamethonium to maximum depression of T_1 was monitored.

The results of the previous study showed that the fourth twitch height was significantly larger than the T_1 height when the TOF responses were measured by acceleromyography and before an injection of neuromuscular blocking agent. Calculation of sample size was based on the averaged baseline TOF ratio was 1.11 (0.09) [mean (SD)] [14], and a significant neuromuscular block induced by precurarization was defined as less than 90% [15] of the baseline TOF ratio ($1.11 \times 0.9 = 0.99$). For the results to have statistical significance with $\alpha = 0.05$ and $\beta = 0.80$, one needed to recruit 10 patients in each group. To allow for dropouts, we enrolled 12 patients in each group. Data are presented as mean (SD). Statistical analysis was performed using StatView software for Windows (SAS Institute, Cary, NC, USA). Analysis of variance was used for multiple comparisons. If a significant P value of <0.05 was obtained in multiple comparisons, further group comparisons were made using the Bonferroni post hoc test. Unpaired Student's t test was used for two-group comparisons. A P value <0.05 was considered statistically significant.

Results

Data from all 24 patients could be included in the analyses. Patient characteristics did not differ between the two groups (Table 1). In 0.03 mg/kg group, an averaged TOF ratio was maintained above 0.9 even 3 min after precurarization (Table 2), and a significant depression in the TOF ratio was shown only in 3 patients, at 2 and 3 min after precurarization, but the ratio was maintained at more than 0.7 (Fig. 1a). In the 0.06 mg/kg group, a significant neuromuscular block was observed in all patients (Fig. 1b),