Target-Controlled Anesthesia Reduces Postoperative Delirium in Spinal Surgical Patients: A Prospective Pilot Study

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The aim of this pilot study was to examine the effect of combined target-controlled anesthesia and manually controlled anesthesia on the incidence of postoperative delirium (POD) in patients undergoing spinal surgery. All of the patients were enrolled before spinal surgery and divided into 2 groups at random: one group received combined sevoflurane target-controlled inhalation and sufentanil target-controlled infusion (S-S TCI group), whereas the other received combined manually controlled sevoflurane inhalation and sufentanil infusion (S-S MCI group). Data related to preoperative factors, perioperative factors, and postoperative data were retrospectively collected. Compared with the S-S MCI group, the dosage of vasoactive drugs after surgery, postoperative recovery time, time to cannula removal, and the incidence of POD were significantly decreased in the S-S TCI group ($P < 0.05$). Overall, POD appeared in 81 patients (16.8%) by postoperative day 3. Multiple regression analysis showed that postoperative blood loss and manually controlled anesthesia were risk factors for POD in spinal surgery patients. Therefore, prophylactic blood transfusion and phenylephrine can reduce the incidence of POD in the presence of postoperative hypotension. Target-controlled anesthesia may improve the quality of anesthesia as well as reduce POD in spinal surgical patients. These results provide clinical evidence for improving the prevention, diagnosis, and management of POD.

Key words: Postoperative delirium – Target-controlled anesthesia – Manually controlled anesthesia – Spinal surgical patients
Delirium is an acute confusional state characterized by fluctuating symptoms that include inattention, disturbances of consciousness, or disorganized thinking. Postoperative delirium (POD) is common in surgical patients and usually occurs 24 to 72 hours after surgery; it resolves within hours to days. In some conditions, POD is often associated with prolonged hospital stay, greater cost of care, additional complications, poor recovery, and even increased mortality rates. Therefore, patients who are predisposed to POD should be identified as early as possible, and necessary preventative interventions should be instituted.

Infusion devices for anesthesia can be controlled either manually, where the anesthetist makes each change to the infusion rate, or in a target-controlled manner, where the anesthetist sets a target concentration and the computerized infusion device makes the necessary changes to the infusion rate. However, the difficulty of monitoring the plasma concentrations of anesthetic agents in patients undergoing manually controlled infusion (MCI) greatly increases when the infusion time is prolonged. According to the pharmacokinetic and pharmacodynamic data of the anesthetics, target-controlled infusions (TCIs) can control the rate of drug injection and make target concentrations in either the plasma or effector compartment stable at the expected value by analogue computation of the disposition and fate of the anesthetic agents, as well as their clinical effects. As a result, TCI can easily control the depth of anesthesia and maintain hemodynamic stability during surgery.

A randomized trial has previously explored differences in the quality of anesthesia, adverse event rates, and costs between these two types of anesthesia. Postoperative hypotension is high risk factor of POD, but the effectiveness of the target-controlled method compared with the manually controlled method on the incidence of POD remains controversial.

In the present, novel study, the effects of TCI and MCI on the incidence of POD in patients undergoing spinal surgery were examined. This study aimed to provide clinical evidence for improving the prevention, diagnosis, and management of POD.

Materials and Methods

Study design

The incidence of POD in our 2-week pilot study was 16.7%, which was similar to the published data. We assumed that the expected positive rate (P) was 16.7%, with a 20% relative error (ε) and a 95% confidence interval [1 − ε] and e equation \[ n = \frac{Z^2_{1-\alpha/2}(1 - P)}{(\varepsilon^2 + P)} \], the current sample size should be 480. All patients were simply divided into two groups at random (n = 240 in each group). A combined sevoflurane target-controlled inhalation and sufentanyl target-controlled infusion group (S-S TCI group) was compared with a group that received anesthesia with the combined manually controlled inhalation of sevoflurane and sufentanyl infusion (S-S MCI group; Fig. 1). Patients were not premedicated and each fasted for at least 6 hours preoperatively. Electrocardiogram, SpO2, heart rate (HR), and noninvasive blood pressure (BP) monitoring were used in the operating theater. The left radial artery was punctured to monitor the mean arterial pressure (MAP), cardiac output and stroke volume variation. The right internal jugular vein was punctured to monitor the central venous pressure.

Patient recruitment

After obtaining approval (no. 2011006) from the hospital research ethics committee and written informed consent from each patient, 480 patients (ages 35–60 years) were enrolled before spinal surgery. All of the patients were American Society of Anesthesiologists grade I or II and were undergoing elective nucleus pulposus removal and laminectomy decompression fixation under general anesthesia. Patients with underlying psychologic diseases, including delirium, depression, or dementia, or patients who had any history of taking hypnotic medications, were excluded.

Anesthesia methods

Surgery and anesthesia were performed by the same group of operators and anesthetists under the same criteria in each patient. In the target-controlled groups, sufentanyl was infused using the TCI system via syringe pumps (Fresenius Kabi Co, Baden Humboldt, Germany). The Gepts pharmacokinetic model for sufentanyl was used. The end tidal concentration of sevoflurane was controlled by the Zeus TCI system (Dräger Co, Lubeck, Germany). In the MCI group, sufentanyl was infused using a common venous pump. Sevoflurane was inhaled through a GS anesthesia machine (Dräger Co) without the use of a TCI system to control the end tidal concentration. General anesthesia was performed according to the group allocation. During

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In the induction period, the target end tidal concentration of sevoflurane inhalation was 1.0% to 3.0%, and the target concentration of sufentanil was 0.2 to 0.3 ng/mL in the S-S TCI group. In the S-S MCI group, sevoflurane was inhaled to maintain an end tidal concentration at 1.0% to 3.0% with a sufentanil infusion of 20 to 30 μg. After the initial loss of consciousness, manual assisted ventilation was administered via a facemask with 100% oxygen. Tidal volume was maintained at 8 to 10 mL/kg with a respiratory rate at 12 to 15 breaths per minute. During the maintenance period, the target end tidal concentration of sevoflurane inhalation was 1.0% to 2.0%, and the target concentration of sufentanil was 0.2 to 0.3 ng/mL in the S-S TCI group; sevoflurane was inhaled to maintain an end tidal concentration at 1.0% to 3.0%, with intermittent intravenous sufentanil infusion at 10 μg each time. In both the TCI and MCI groups, cisatracurium besylate was infused in all patients at 0.1 mg/kg/h. During surgery, the partial pressure of end tidal carbon dioxide (P_{ET}CO_2) was maintained at 30 to 40 mmHg. The variation of HR and MAP was no higher than 20% compared with the corresponding baseline value before surgery.

In the present study, we measured the depth of anesthesia using the BP, HR, and bispectral index (BIS) values. We maintained the value of BIS at 40 to 55 during surgery. The end tidal sevoflurane concentration in the 2 groups was adjusted according to the BP, HR, and BIS values. Adjustment principles of sevoflurane and vasoactive drugs during surgery are shown in Table 1.

Clinical outcomes

The primary outcomes were POD and predefined risk factors in patients under spinal surgery. The Confusion Assessment Method (CAM) was used to diagnose POD. This tool assesses the presence, severity, and fluctuation of 9 features of delirium: acute onset, inattention, disorganized thinking, altered level of consciousness, disorientation, memory impairment, perceptual disturbances, psychomotor agitation or retardation, and an altered sleep-wake cycle. Features 1 (acute onset and fluctuating course) and 2 (inattention) are essential features, whereas features 3 (disorganized thinking) and 4 (altered level of consciousness) are supported by expert

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**Fig. 1** The flow diagram for the study.
judgments and clinical examination. The first two features and either of the latter two features were required for the diagnosis of POD. The evaluation of cognitive dysfunction was blinded, because the experts who evaluated cognitive dysfunction did not know which method of anesthesia the patients had received. Confusion Assessment Method was continued once a day for 3 days once delirium was diagnosed.

**Data analysis**

Data related to preoperative factors (e.g., age, male sex, body mass index, and previous job type), perioperative factors (e.g., duration of surgery, amount of blood loss, blood transfused, and dose of vasoactive drugs), and postoperative data (e.g., recovery time, time of cannula removal after surgery, and POD) were retrospectively collected and statistically analyzed using SPSS 16.0 software (SPSS Inc, Chicago, Illinois). Values were expressed as the means ± SD for continuous variables, or as percentages of the group from which they were derived for categoric variables. The 2-sample t-test was used for the statistical analysis of differences between the 2 groups, and the \( \chi^2 \) test was used to compare the categoric data. Multiple logistic regression analysis was performed to find the risk factors of POD in spinal surgical patients, including all factors that were independent variables. \( P < 0.05 \) was considered to be statistically significant.

**Results**

Differences of the demographic features and relative factors between patients managed with target-controlled and manually controlled anesthesia undergoing spinal surgery

The mean age of the 480 patients recruited was 51.4 ± 8.1 years. Male patients accounted for 56.2%. Table 2 shows the comparison between the target-controlled and manually controlled groups. There was no significant difference in demographic features, duration of surgery, amount of blood loss, and amount of blood transfused between the S-S TCI group and the S-S MCI group (\( P > 0.05 \)). The amount of sevoflurane used was significantly lower, whereas the amount of sufentanil was significantly higher during surgery in the TCI group (\( P < 0.05 \)). With regard to the medication requirement during sur-

| Group                                | Total (n = 480) | S-S TCI (n = 240) | S-S MCI (n = 240) | \( P \) value |
|--------------------------------------|----------------|------------------|------------------|--------------|
| Male sex, n (%)                      | 270 (56.2)     | 131 (54.6)       | 139 (57.9)       | 0.218        |
| Age, y, mean ± SD                    | 51.4 ± 8.1     | 52.3 ± 7.3       | 49.3 ± 10.2      | 0.243        |
| Manual worker, n (%)                 | 119 (24.8)     | 62 (25.8)        | 57 (23.8)        | 0.195        |
| Duration of surgery, min, mean ± SD | 245.4 ± 56.1   | 248.8 ± 53.6     | 239.5 ± 58.3     | 0.126        |
| Amount of blood loss, mL, mean ± SD | 1920.6 ± 425.8 | 1891.3 ± 442.5   | 1942.2 ± 417.4   | 0.097        |
| Amount of blood transfused, mL, mean ± SD | 1773.1 ± 572.6 | 1726.6 ± 384.8  | 1786.4 ± 366.8   | 0.093        |
| Phenylephrine during surgery, % (n)  | 20.4 (98)      | 10.4 (25)        | 30.4 (73)        | 0.382*       |
| Esmolol during surgery, % (n)        | 33.3 (160)     | 20 (48)          | 46.6 (112)       | 0.411*       |
| Sufentanil, \( \mu \)g, mean ± SD   | 64.6 ± 14.2    | 72.5 ± 16.4      | 55.8 ± 11.5      | 0.049*       |
| Sevoflurane, mL, mean ± SD           | 22.5 ± 6.7     | 13.4 ± 4.2       | 31.6 ± 7.5       | 0.022*       |
| Recovery time, min, mean ± SD        | 16.5 ± 4.6     | 8.4 ± 2.2        | 20.1 ± 3.6       | 0.021*       |
| Time of cannula removal, min, mean ± SD | 13.9 ± 2.4   | 6.7 ± 2.1        | 18.7 ± 3.1       | 0.014*       |
| POD within 3 days after surgery, % (n) | 16.8 (81)      | 7.5 (18)         | 26.2 (63)        | 0.033*       |

*\( P < 0.05 \).
gery, more patients in the MCI group were given phenylephrine and esmolol than in the TCI group \((P < 0.05)\). After surgery, the duration of recovery time and the timing of cannula removal were significantly shorter in the TCI group \((P < 0.05)\). In terms of POD, the incidence was also significantly lower in the TCI group compared with the MCI group \((P < 0.05)\).

**Differences in demographic features and relative factors between patients with and without POD undergoing spinal surgery**

POD was defined as delirium occurring within a period of 3 postoperative days, and it was identified in 81 patients \((16.8\%)\) among the whole cohort. A comparison of patients with POD \((n = 81)\) and without \((n = 399)\) POD is shown in Table 3. The patients with POD tended to be older \((P > 0.05)\) than those without POD. Compared with those without POD, the patients with POD experienced longer durations of surgery, with higher volumes of blood loss requiring larger blood transfusions \((P < 0.05)\). With regard to the medication requirement during surgery, more patients with POD were given phenylephrine and esmolol than those without POD \((P < 0.05)\). After surgery, the recovery time was significantly shorter and the time of cannula removal was significantly shorter in patients without POD compared with those with POD \((P < 0.05)\). The percentage of patients with MCI in the POD group was 77.7\%, which was significantly higher than the percentage of patients with MCI in the non-POD group \((P < 0.05)\).

**Risk factors for POD in patients undergoing spinal surgery**

Multiple regression analysis found that increased volumes of blood loss postoperatively and manually controlled anesthesia were independent risk factors for POD \((P < 0.05)\). Postoperative blood transfusion and intraoperative phenylephrine were protective factors for reducing POD when postoperative hypotension had occurred (Table 4).

**Discussion**

As a result of the side effects of POD, its prevention, early diagnosis, and treatment have been great

### Table 3 Comparisons between patients with and without POD

| Group                              | POD \((n = 81)\) | Non-POD \((n = 399)\) | \(P\) value |
|------------------------------------|-----------------|-----------------------|-------------|
| Male sex, \% (n)                   | 53.1 (43)       | 56.8 (227)            | 0.271       |
| Manual worker, \% (n)              | 27.1 (22)       | 24.3 (97)             | 0.367       |
| Age, y, mean ± SD                  | 52.1 ± 8.2      | 44.3 ± 7.4            | 0.057       |
| Duration of surgery, min, mean ± SD| 315.3 ± 74.6    | 233.7 ± 60.5          | 0.041*      |
| Amount of blood loss, mL, mean ± SD| 2438.6 ± 488.3  | 1821.2 ± 454.7        | 0.045*      |
| Amount of blood transfused, mL, mean ± SD| 2124.3 ± 422.6 | 1648.7 ± 369.3        | 0.046*      |
| Phenylephrine during surgery, \% (n)| 59.2 (48)       | 10.0 (40)             | 0.031*      |
| Esmolol during surgery, \% (n)     | 51.9 (42)       | 29.5 (118)            | 0.049*      |
| Sufentanil, \(\mu g\), mean ± SD  | 62 ± 13         | 67 ± 12               | 0.812       |
| Sevoflurane, mL, mean ± SD         | 26 ± 6          | 23 ± 7                | 0.863       |
| Time of cannula removal, min, mean ± SD| 12.8 ± 2.1     | 7.5 ± 1.9             | 0.043*      |
| Recovery time, min, mean ± SD      | 22.5 ± 4.2      | 17.4 ± 3.6            | 0.031*      |
| Manually controlled anesthesia, \% (n)| 77.7 (63)       | 44.3 (177)            | 0.029*      |

\(*P < 0.05.*

### Table 4 Results of logistic regression to ascertain the risk factors for POD

|                                             | B    | SE  | Wald  | Sig.   | Exp(B) |
|---------------------------------------------|------|-----|-------|--------|--------|
| Duration of surgery (min)                   | 1.001| 0.304| 8.034 | 0.049* | 1.984  |
| Amount of blood loss (mL)                   | 1.165| 0.332| 8.247 | 0.044* | 2.458  |
| Amount of blood transfused (mL)             | -1.237| 0.316| 20.145| 0.048* | 0.446  |
| Phenylephrine during surgery, \% (n)        | -1.002| 0.289| 18.352| 0.043* | 0.665  |
| Esmolol during surgery, \% (n)              | -0.446| 0.121| 4.251 | 0.085  | 0.653  |
| Time of cannula removal (min)               | 0.437| 0.132| 2.335 | 0.933  | 1.078  |
| Recovery time (min)                         | 0.528| 0.137| 2.869 | 0.917  | 1.165  |
| Manually controlled anesthesia, \% (n)      | 1.041| 0.323| 7.983 | 0.012* | 3.198  |

\(*P < 0.05.*
challenges for anesthetists. In previously published reports, POD has been shown to develop in 10% to 60% of patients, and the rate of occurrence is most frequent in the elderly (age ≥65 years). As a result, we selected patients ages 35 to 60 years in order to exclude the influence of age on the results. The incidence in our study population (16.8%) appears to be relatively lower than the above published rates, which may be partly correlated with the relatively younger age of our recruited patients. Additionally, patients with preoperative depression, dementia, or delirium were excluded from our study. Kaneko et al previously found that preoperative cognitive impairment was a risk factor for POD. Thus, the exclusion of the patients with preoperative dementia may reduce the incidence of POD to some extent. The incidence of POD has also been reported in several types of surgery; however, reports with regard to POD in spinal surgery are very scarce. Kawaguchi et al reported that the incidence of POD in spinal surgery was 12.5%. Another paper suggested that POD in spinal surgery can also occur in younger patients. An operative duration >10 hours, blood transfusions of >800 mL, and a transfusion of >5000 mL were considered to be significant risk factors in the study by Yamagata et al. In this study, there was no significant difference in patient age, type of surgery, operative time, intraoperative blood loss, and intraoperative blood transfusion volumes between the 2 groups, which made the results of the 2 groups comparable. The incidence of POD (16.8%) in our study was higher than previously reported in spinal surgery, but it was still relatively lower than that found in other types of surgeries. Furthermore, we found that the incidence of POD (7.5%) in S-S TCI group was even lower. Considering the paucity of papers in this field, more studies are required to investigate POD in patients undergoing spinal surgery.

POD has been related to many risk factors, including (1) preoperative factors, such as patient age, drug use, sensory impairment, and comorbidities; (2) intraoperative factors, such as the type of surgery, type of anesthesia, duration of surgery, blood loss, and amount of blood transfused; and (3) postoperative factors, such as laboratory data, blood pressure, and opiate analgesic drug use. Our study verified the association between a longer recovery time and manually controlled anesthesia with POD after spinal surgery. Combined target-controlled infusion or inhalation was administered in order to investigate its effect on POD in patients undergoing spinal surgery for the first time; these results proved to be encouraging. In our study, fluctuations in the blood pressure of patients in both groups were within 20% of the baseline level. The number of patients who required vasoactive drugs in the TCI group was lower than in the MCI group, which might have been a result of the suitable maintenance of analgesic depth using sufentanil via a TCI. In the MCI group, it was hard to maintain suitable plasma concentrations of the anesthetic agents to meet the analgesic demand by a single additional sufentanil infusion during surgery. In contrast, TCI enabled the administration of a full anesthesia that could precisely control the end tidal sevoflurane concentration, in addition to the advantages of rapid induction, deepening, reduction of light anesthesia, and lower volumes of sevoflurane in the TCI group compared with the MCI group. Furthermore, the incidence of POD in the TCI group was lower than in the MCI group during spinal surgery, which indicates that target-controlled anesthesia in itself may protect patients from developing POD. Considering the high incidence of POD in surgical patients, we suggest that target-controlled anesthesia might be used more widely in patients at high risk of developing POD.

There were limitations in this study. First, data regarding certain potential risk factors, such as blood glucose, blood pressure, and sodium levels, were not collected in this study. Second, the study was performed within a single hospital. To verify the contribution of target-controlled anesthesia in the prevention of POD, prospective studies that include multiple centers will be required. It might be difficult to ascertain whether the differences in outcome between groups resulted from the TCI of sufentanil only, or the target-controlled inhalation of sevoflurane. Thus, this retrospective study can only be considered as a pilot study to give clinical evidence for the importance of combined target-controlled anesthesia for patients undergoing spinal surgery.

In general, our study found an incidence of POD of 16.8% in patients undergoing spinal surgery. Our findings indicated that target-controlled anesthesia had a protective effect against POD in spinal surgical patients. These results may help improve the prevention, diagnosis, and management of POD in patients undergoing spinal surgery. However, further prospective research is necessary to evaluate the full range of potential confounding and predictive factors in greater detail.
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