

# Effects of dexmedetomidine vs sufentanil during percutaneous tracheostomy for traumatic brain injury patients

## A prospective randomized controlled trial

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### Abstract

**Background:** Percutaneous tracheostomy, almost associated with cough reflex and hemodynamic fluctuations, is a common procedure for traumatic brain injury (TBI) patients, especially those in neurosurgery intensive care units (NICUs). However, there are currently a lack of effective preventive measures to reduce the risk of secondary brain injury. The aim of this study was to compare the effect of dexmedetomidine (DEX) vs sufentanil during percutaneous tracheostomy in TBI patients.

**Methods:** The 196 TBI patients who underwent percutaneous tracheostomy were randomized divided into 3 groups: group D1 (n = 62, DEX infusion at  $0.5 \mu\text{g}\cdot\text{kg}^{-1}$  for 10 minutes, then adjusted to  $0.2\text{--}0.7 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ ), group D2 (n = 68, DEX infusion at  $1 \mu\text{g}\cdot\text{kg}^{-1}$  for 10 minutes, then adjusted to  $0.2\text{--}0.7 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ ), and group S (n = 66, sufentanil infusion  $0.3 \mu\text{g}\cdot\text{kg}^{-1}$  for 10 minutes, then adjusted to  $0.2\text{--}0.4 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ ). The bispectral index (BIS) of all patients was maintained at 50 to 70 during surgery. Anesthesia onset time, hemodynamic variables, total cumulative dose of DEX/sufentanil, total doses of rescue propofol and fentanyl, time to first dose of rescue propofol and fentanyl, number of intraoperative patient movements and cough reflexes, adverse events, and surgeon satisfaction score were recorded.

**Results:** Anesthesia onset time was significantly lower in group D2 than in both other groups ( $14.35 \pm 3.23$  vs  $12.42 \pm 2.12$  vs  $13.88 \pm 3.51$  minutes in groups D1, D2, and S, respectively;  $P < .001$ ). Both heart rate and mean arterial pressure during percutaneous tracheostomy were more stable in group D2. Total doses of rescue propofol and fentanyl were significantly lower in group D2 than in group D1 ( $P < .001$ ). The time to first dose of rescue propofol and fentanyl were significantly longer in group D2 than in both other groups ( $P < .001$ ). The number of patient movements and cough reflexes during percutaneous tracheostomy were lower in group D2 than in both other groups ( $P < .001$ ). The overall incidences of tachycardia and hypertension (which required higher doses of esmolol and urapidil, respectively) were also lower in group D2 than in both other groups ( $P < .05$ ). Three patients in group S had respiratory depression compared to X in the D1 group and X in the D2 group. The surgeon satisfaction score was significantly higher in group D2 than in both other groups ( $P < .05$ ).

**Conclusions:** During percutaneous tracheostomy, compared with sufentanil, DEX ( $1 \mu\text{g}\cdot\text{kg}^{-1}$  for 10 minutes, then adjusted to  $0.2\text{--}0.7 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$ ) can provide the desired attenuation of the hemodynamic response without increased adverse events. Consequently, DEX could be used safely and effectively during percutaneous tracheostomy in TBI patients.

**Abbreviations:** ASA = American Society of Anesthesiologists, BIS = bispectral index, CBF = cerebral blood flow, CMRe = cerebral metabolic rate equivalent, DBP = diastolic blood pressure, FiO<sub>2</sub> = fraction of inspired oxygen, GABA = gamma-aminobutyric acid, GCS = glasgow coma scale, HR = heart rate, IQR = inter-quartile range, MAP = mean arterial pressure, NICUs = neurosurgery intensive care units, PaO<sub>2</sub> = pressure of oxygen, PbtO<sub>2</sub> = partial pressure of brain tissue oxygen, PSH = Paroxysmal sympathetic hyperactivity, PSH-AM = PSH Assessment Measure, SBP = systolic blood pressure, SpO<sub>2</sub> = saturation of peripheral oxygen, TBI = traumatic brain injury, TH = therapeutic hypothermia, TTM = targeted temperature management.

**Keywords:** dexmedetomidine, monitored anesthesia care, percutaneous tracheostomy, sufentanil, traumatic brain injury

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## 1. Introduction

Traumatic brain injury (TBI) is a serious medical problem worldwide. The annual number of new TBI patients in the United States is 1.7 million, with >257,000 requiring hospitalization and 50,000 deaths. The cost of TBI in the United States in 2013 was estimated to be \$13.1 billion, and an additional \$51.2 billion is lost because of missed work and lost productivity.<sup>[1]</sup> TBI represents a principal cause of death and disability in patients aged <35 years in the United States.<sup>[2]</sup> The high mortality rate associated with TBI may be due to the highly variable pathologies involved, such as neuroinflammation, neurotransmitter imbalances, and structural and functional brain damage.<sup>[3,4]</sup> As a result, there are more and more organizations providing guidelines on perioperative care and management of severe TBI.<sup>[5,6]</sup>

Percutaneous tracheostomy is one of the most commonly conducted procedures for TBI patients, especially in neurosurgery intensive care units (NICUs). It has many potential advantages, such as improving nursing care and tolerability and reducing rates of laryngeal edema and oral infection.<sup>[7]</sup> However, percutaneous tracheostomy is almost associated with cough reflex and fluctuation of hemodynamics, which can increase intracranial pressure and eventually affect prognosis.<sup>[8]</sup> As a result, percutaneous tracheostomy has been performed with a combination of local and intravenous anesthesia/sedation to promote patient comfort. The most commonly used drugs include opiates, benzodiazepines, and propofol. However, each of these drugs has its own limitations, such as significant respiratory depression and loss of protective airway reflexes, which can increase the risk of poor neurological outcomes in TBI patients.<sup>[9,10]</sup> Hence, an ideal sedative and analgesic drug with limited adverse effects for use during percutaneous tracheostomy in TBI patients is urgently needed.

Dexmedetomidine (DEX), which has sedative, analgesic, and anxiolytic properties and does not cause respiratory depression, has been widely used in anesthesia and in intensive care units.<sup>[11]</sup> Previous research has also shown that DEX can reduce sympathetic nerve tension during laryngoscopy and tracheal intubation.<sup>[12]</sup> However, there are few studies on the sympathetic nervous system response during percutaneous tracheostomy. The purpose of this study was to compare the effect of DEX vs sufentanil during percutaneous tracheostomy in TBI patients.

## 2. Materials and methods

### 2.1. Patients

We obtained approval for this trial from the Institutional Review Board of Liaocheng People's Hospital, and the trial was registered at [chictr.org](http://chictr.org) (ChiCTR-IPR-16008494). All the patients' guardians signed informed consent forms. TBI patients who underwent percutaneous tracheostomy with sufentanil or DEX between August 2016 and December 2018 were enrolled in this study if they met the following inclusion criteria: aged 40 to 65 years with severe TBI (Glasgow Coma Scale [GCS]  $\leq 8$ ). The exclusion criteria were as follows: history of hypertension (mean arterial pressure [MAP]  $>110$  mmHg, systolic blood pressure [SBP]  $>160$  mmHg, or diastolic blood pressure [DBP]  $>90$  mmHg); hypotension (MAP  $<70$  mmHg, SBP  $<90$  mmHg, or DBP  $<50$  mmHg); bradycardia (heart rate [HR]  $<50$  beats/minute); hypoxemia (partial pressure of oxygen [PaO<sub>2</sub>]  $<60$  mmHg or saturation of peripheral oxygen [SpO<sub>2</sub>]  $<90\%$ ); second- or third-degree heart block; long-term ( $>6$  months) abuse of or addiction to alcohol, tobacco, opioids, or sedative-hypnotic drugs; allergy to study drugs; serious hepatic dysfunction (Child-Pugh class B or C); and serious renal dysfunction (serum creatinine  $>445$  mmol/L and/or blood urea nitrogen  $>20$  mmol/L).

### 2.2. Percutaneous tracheostomy

No premedication was administered before surgery. Electrocardiography, noninvasive arterial blood pressure, SpO<sub>2</sub>, and axillary temperature were monitored (IntelliVue MP50 Patient Monitor; Philips) according to the American Society of Anesthesiologists (ASA) standardized guidelines.<sup>[13]</sup> Oxygen supplementation at 5 L·minute<sup>-1</sup> was achieved using an oxygen face mask. A forced-air warming device (Bair Hugger 750;

Germany) was also used during the surgery to maintain normothermia. Patients in groups D1 and D2 received a loading dose of 0.5 or 1.0  $\mu\text{g}\cdot\text{kg}^{-1}$  DEX over 10 minutes, respectively, followed by a maintenance infusion of 0.2 to 0.7  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$  during surgery. Patients in group S received a loading dose of 0.3  $\mu\text{g}\cdot\text{kg}^{-1}$  sufentanil over 10 minutes followed by a maintenance infusion of 0.2 to 0.4  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hour}^{-1}$  during surgery. The target score of the 3 groups was a Bispectral Index (BIS; Model A2100; Covidien, Mansfield, MA) of 50 to 70, based on the results of a previous study.<sup>[14]</sup>

The percutaneous tracheostomies<sup>[15]</sup> were performed in an identical fashion by neurosurgeons with  $\geq 5$  years of residency experience. Planned incision sites were injected with 1% lidocaine with epinephrine at a ratio of 1:100,000. Once an airway was established after exposure of the tracheal rings, an endotracheal tube was placed and confirmed by capnography. The tube was secured in place with two 0 silk sutures and tracheostomy ties. During the surgery, 0.5  $\text{mg}\cdot\text{kg}^{-1}$  propofol was given repeatedly every 5 minutes if BIS  $>70$ , and 1  $\mu\text{g}\cdot\text{kg}^{-1}$  fentanyl was administered repeatedly every 5 minutes if the patient moved.

### 2.3. Adverse events

Coughing after tracheal intubation was assessed using a 5-point scale, as reported in a previous study:

- (1) no cough, easy breathing;
- (2) slight coughing (1 or 2), easy breathing;
- (3) moderate coughing (3 or 4);
- (4) heavy coughing, breathing hard; and
- (5) laryngospasm, severe coughing, or hardly breathing.<sup>[8]</sup>

Hypertension (MAP  $>110$  mmHg or SBP  $>160$  mmHg) was treated with urapidil (10–15 mg). Hypotension (MAP  $<70$  mmHg or SBP  $<110$  mmHg) was treated with an intravenous bolus of ephedrine (6–12 mg) or phenylephrine (20–40  $\mu\text{g}$ ). Bradycardia (HR  $<50$  beats/minute) was treated with atropine (0.2–0.4 mg). Tachycardia (HR  $>120$  beats/minute) was treated with esmolol (20–30 mg). Hypoxia was treated with supplemental oxygen or by increasing the fraction of inspired oxygen (FiO<sub>2</sub>). Respiratory depression (respiratory rate  $<8$  breaths/minute or SpO<sub>2</sub>  $<90\%$ ) was treated with physical stimulation, naloxone, or positive pressure ventilation.<sup>[16]</sup>

### 2.4. Outcome variables

Preoperative, intraoperative, and postoperative variables were reviewed using an electronic chart and DoCare Clinic electronic anesthesia recording system. Hemodynamic variables (MAP and HR) were measured at T0, T1, T2, T3, T4, T5, T6, and T7, which were defined as at arrival at the operation room, at the start of infusion, after bolus administration of drug, before local anesthetic, before skin incision, at tracheal intubation, at 5 minutes after tracheal intubation, and at 10 minutes after tracheal intubation, respectively. Paroxysmal sympathetic hyperactivity (PSH) score, anesthesia onset time, duration of anesthesia and surgery, total cumulative dose of DEX/sufentanil, time to first dose of rescue propofol and fentanyl, total doses of rescue propofol and fentanyl, number of intraoperative patient movements, surgeon satisfaction score, and adverse events (such as bradycardia, tachycardia, hypotension, hypertension, and respiratory depression) were also recorded.

## 2.5. Statistical analysis

The Kolmogorov–Smirnov test was used to assess the distribution of variables. Homogeneity of variance was determined using Levene test. Continuous data were expressed as mean and standard deviation or median and inter-quartile range (IQR), depending on whether the data were normally distributed. For normally distributed continuous variables, inter-group comparisons were performed using repeated-measures analysis of variance. The Bonferroni correction was used for post-hoc multiple comparisons. For non-normally distributed continuous variables, inter-group comparisons were performed using the nonparametric Kruskal–Wallis test. Categorical data were expressed as frequency and percentage and analyzed using chi-square tests or Fisher exact tests, when appropriate. *P* values <.05 were considered statistically significant. Statistical analysis was performed with SPSS for Windows version 23.0 (SPSS Inc., Chicago, IL).

## 3. Results

### 3.1. Baseline characteristics

Figure 1 shows a flow diagram of patient enrollment. The 293 TBI patients who underwent percutaneous tracheostomy were

screened between August 2016 and December 2018. Based on the inclusion/exclusion criteria, 97 patients were excluded: 23 patients had a history of hypertension; 5 had a history of hypotension; 2 had bradycardia; 12 had hypoxemia; 4 had second- or third-degree heart block; 22 had long-term abuse of or addiction to alcohol, tobacco, opioids, or sedative-hypnotic drugs; 1 was allergic to the study drugs; 3 had a history of serious hepatic dysfunction; 2 had a history of renal dysfunction; and 23 had incomplete clinical data. Finally, 196 patients were included and divided into 3 groups. Demographic variables were not significantly different among the 3 groups ( $P > .05$ , Table 1).

### 3.2. Intraoperative variables

There were no significant differences among the three groups with respect to baseline variables ( $P > .05$ , Fig. 2). Compared with group S, both HR and MAP in groups D1 and D2 were significantly decreased at T4, T5, and T6 ( $P < .05$ , Fig. 2). The lowest HR and MAP values in the 3 groups all occurred at T3.

Anesthesia onset time was significantly shorter in group D2 ( $15.36 \pm 4.23$  vs  $15.42 \pm 3.12$  vs  $13.98 \pm 2.58$  minutes in groups S, D1, and D2, respectively,  $P < .001$ , Table 2), and durations of

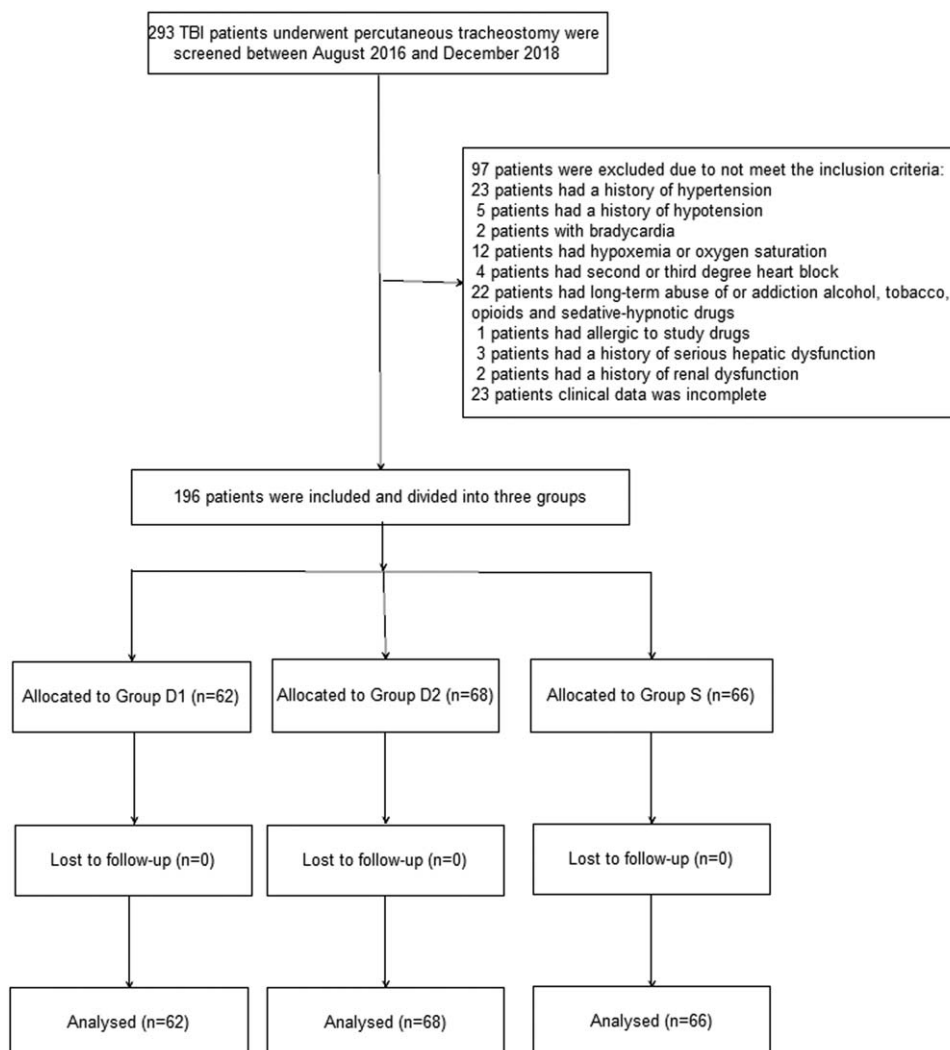


Figure 1. Flow diagram of patient enrollment.

**Table 1**  
Demographic parameters among the 3 groups.

| Variable                  | Group S (n = 66) | Group D1 (n = 62) | Group D2 (n = 68) | P values |
|---------------------------|------------------|-------------------|-------------------|----------|
| Age (yr)                  | 52.53 ± 9.33     | 55.02 ± 8.92      | 55.89 ± 7.92      | .073     |
| Body weight (kg)          | 68.39 ± 8.43     | 71.83 ± 9.34      | 70.98 ± 7.20      | .052     |
| Sex (male/female)         | 40/26            | 43/19             | 41/27             | .485     |
| BMI (kg m <sup>-2</sup> ) | 23.09 ± 3.12     | 22.02 ± 2.92      | 22.87 ± 2.78      | .099     |
| Preoperative GCS          | 7.78 ± 1.09      | 7.88 ± 0.92       | 7.82 ± 1.03       | .856     |
| PSH score                 | 10.37 ± 3.23     | 9.31 ± 3.04       | 9.39 ± 3.19       | .104     |
| Comorbidity, n (%)        |                  |                   |                   | .982     |
| Arrhythmia                | 2 (3.03%)        | 3 (4.84%)         | 5 (7.35%)         |          |
| Diabetes mellitus         | 22 (33.33%)      | 19 (30.65%)       | 24 (35.29%)       |          |
| COPD/asthma               | 3 (4.55%)        | 3 (4.84%)         | 4 (5.88%)         |          |
| Anemia                    | 7 (10.61%)       | 9 (14.52%)        | 11 (16.18%)       |          |

Variables presented as mean ± SD or number of patients n (%). BMI = body mass index, COPD = chronic obstructive pulmonary disease, GCS = Glasgow Coma Scale.

anesthesia and surgery were also significantly shorter in group D2 ( $P < .05$ , Table 2).

More patients in groups D1 and S compared with group D2 required rescue propofol to maintain BIS at 50 to 70 (66.67% vs 42.67% vs 32.35% in groups S, D1, and D2, respectively,  $P < .001$ , Fig. 3A). However, the total dose of rescue propofol was significantly higher in group S than in groups D1 and D2 ( $1.5 \pm 0.4$  vs  $1.1 \pm 0.3$  vs  $0.9 \pm 0.4$  mg·kg<sup>-1</sup> in groups S, D1, and D2,

respectively,  $P < .001$ , Fig. 3A). The time to first dose of rescue propofol was significantly longer in group D2 than groups D1 and S ( $12.32 \pm 4.47$  vs  $13.56 \pm 5.36$  vs  $16.55 \pm 4.91$  minutes in groups S, D1, and D2, respectively,  $P < .001$ , Table 2).

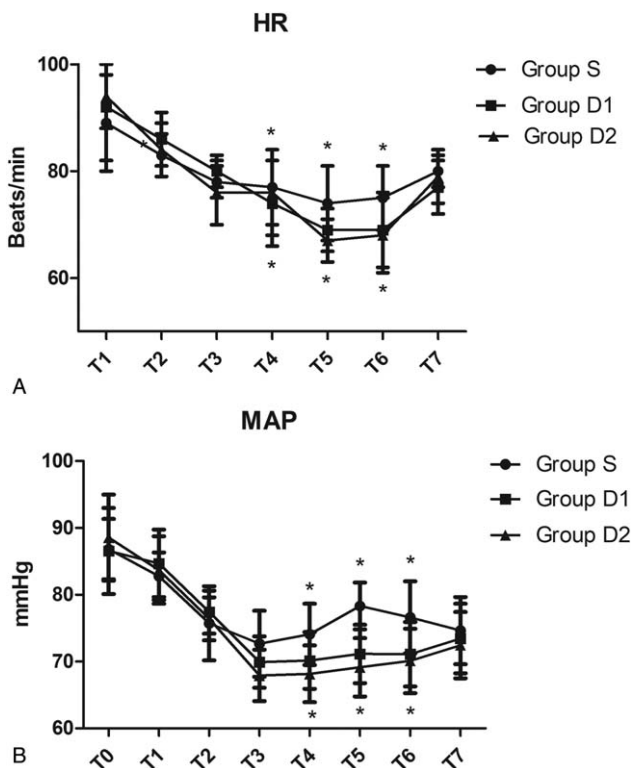
Compared with group D1, significantly fewer patients in groups S and D2 required rescue fentanyl (27.27% vs 40.32% vs 22.06% in groups S, D1, and D2, respectively,  $P < .001$ , Fig. 3B). Additionally, the total dose of rescue fentanyl in group D1 was significantly higher than in groups S and D2 ( $1.5 \pm 0.4$  vs  $2.0 \pm 0.6$  vs  $1.2 \pm 0.2$  μg·kg<sup>-1</sup> in groups S, D1, and D2, respectively,  $P < .001$ , Fig. 3B). The time to first dose of rescue fentanyl was significantly longer in group D2 than groups D1 and S ( $16.47 \pm 3.74$  vs  $12.56 \pm 2.92$  vs  $15.74 \pm 3.65$  minutes in groups S, D1, and D2, respectively,  $P < .001$ , Table 2).

The total number of patient movements during percutaneous tracheostomy was higher in groups D1 and S compared to group D2 (68.18% vs 72.58% vs 36.76% in groups S, D1, and D2, respectively,  $P < .001$ ; Table 2). The surgeon satisfaction score was also significantly different among the three groups ( $P < .05$ , Table 2).

Compared with the incidence of adverse events in the other 2 groups, patients in group D2 had a lower incidence of tachycardia (27.27% vs 24.19% vs 13.24% in groups S, D1, and D2, respectively,  $P = .038$ , Table 3), hypertension (22.73% vs 22.58% vs 11.76% in groups S, D1, and D2, respectively,  $P = .017$ , Table 3), and respiratory depression (7.58% vs 4.84% vs 1.47% in groups S, D1, and D2, respectively,  $P = .013$ , Table 3). The percentages of patients with bradycardia and hypotension during surgery were comparable among the three groups ( $P > .05$ , Table 3). There were also no significant differences among the 3 groups with respect to both the incidence of coughing and coughing grade ( $P > .05$ , Tables 3 and 4).

#### 4. Discussion

Compared with sufentanil, DEX infusion at  $1.0$  μg·kg<sup>-1</sup> (rather than  $0.5$  μg·kg<sup>-1</sup>) for 10 minutes, then adjusted to  $0.2$  to  $0.7$  μg·kg<sup>-1</sup>·hour<sup>-1</sup>, decreases the number of intraoperative patient movements. This may be the primary reason for the better mean surgeon satisfaction score in group D2. The hemodynamic response during percutaneous tracheostomy was also better controlled in group D2. Accordingly, patients in group D2 had lower incidences of tachycardia and hypertension. The incidence of respiratory depression was also different among the 3 groups,



**Figure 2.** Hemodynamics were monitored in the three groups. (A) Comparison of heart rates (HR) (beats/minute) in the 3 groups at different time points. (B) Comparison of mean arterial pressure (MAP) (mmHg) in the 3 groups at different time points. T<sub>0</sub>: arrival at the operation room, T<sub>1</sub>: at the start of infusion, T<sub>2</sub>: after bolus administration of drug, T<sub>3</sub>: before local anesthetic, T<sub>4</sub>: before skin incision, T<sub>5</sub>: at tracheal intubation, T<sub>6</sub>: 5 minutes after tracheal intubation, and T<sub>7</sub>: 10 minutes after tracheal intubation. \* $P < .05$  vs Group S.

**Table 2**  
**Comparison of intraoperative variables among the 3 groups.**

| Variable                                    | Group S (n=66)   | Group D1 (n=62)             | Group D2 (n=68)                 | P values |
|---|------------------|-----------------------------|---------------------------------|----------|
| Anesthesia onset time (min)                 | 15.36 ± 4.23     | 15.42 ± 3.12                | 13.98 ± 2.58 <sup>*,†</sup>     | .023     |
| Duration of anesthesia (min)                | 34.23 ± 4.24     | 32.29 ± 4.74                | 22.89 ± 5.24 <sup>*,‡</sup>     | .001     |
| Duration of surgery (min)                   | 17.24 ± 5.83     | 16.29 ± 4.20                | 11.93 ± 5.06 <sup>*,†</sup>     | .001     |
| Time to first dose of rescue propofol (min) | 12.32 ± 4.47     | 13.56 ± 5.36                | 16.55 ± 4.91 <sup>*,†</sup>     | .001     |
| Time to first dose of rescue fentanyl (min) | 16.47 ± 3.74     | 12.56 ± 2.92 <sup>*,‡</sup> | 15.74 ± 3.65                    | .001     |
| Total patient movements, n (%)              | 45 (68.18%)      | 45 (72.58%)                 | 25 (36.76%) <sup>*,†</sup>      | .001     |
| Surgeon satisfaction score                  | 2.75 (2.25–3.75) | 3.00 (2.25–4.00)            | 4.00 (2.75–5.00) <sup>*,†</sup> | .022     |

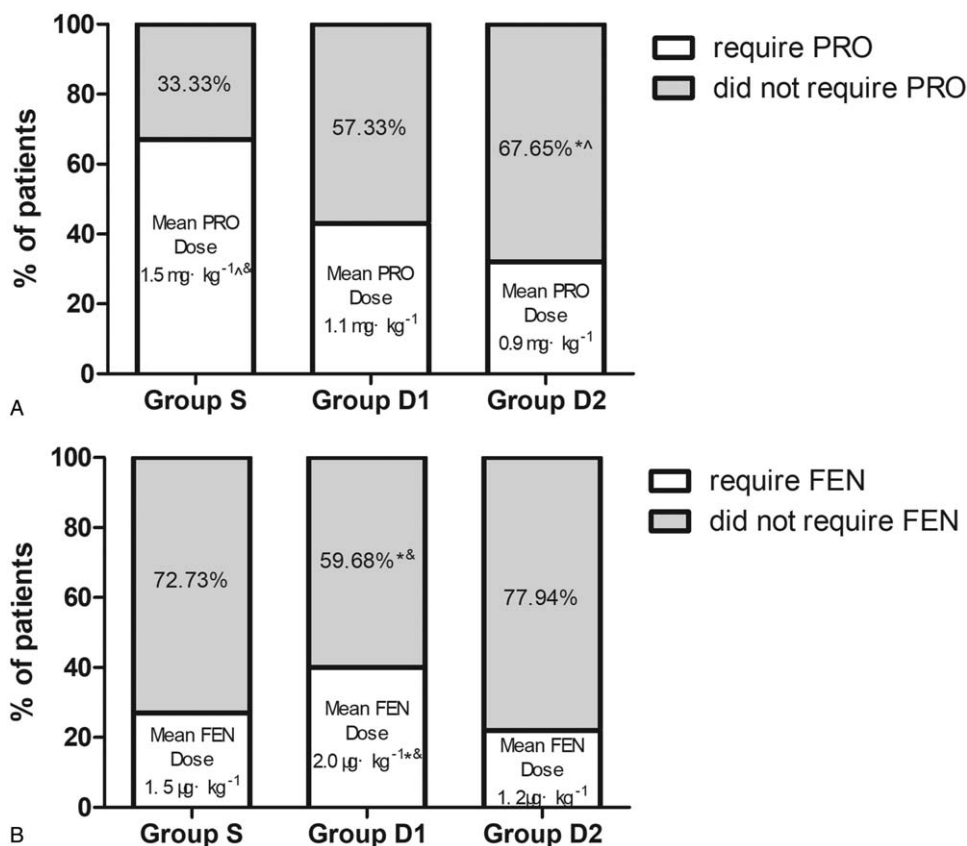
Variables presented as mean ± SD or number of patients n (%).

<sup>\*</sup> P < .05 vs Group S.  
<sup>†</sup> P < .05 vs Group D1.  
<sup>‡</sup> P < .05 vs Group D2.

with a lower incidence in group D2, which may be due to the lower doses of rescue propofol and fentanyl used in group D2.

The principle of TBI management is to ensure stable hemodynamics, adequate oxygenation, and balanced electrolytes, and to prevent secondary brain injury, such as injuries caused by intracranial hypertension, hyperglycemia, and cerebral hypoperfusion.<sup>[17]</sup> Although many therapeutic strategies, such as sedatives, analgesics, beta-blocker and ACE-inhibitor have been proposed, there remains a lack of robust evidence to support a standardized approach to the diagnosis, prognostication, and treatment of TBI.<sup>[18]</sup> Therefore, more mechanistic studies are warranted. Recently, the treatment strategy has been

focused on using multitargeted pharmacological agents as early intervention to reduce the cascade of secondary brain injury.<sup>[19]</sup> Previous research has reported that prolonged ventilation requirements make up to 80% of TBI patients prone to pulmonary complications; chest physiotherapy and tracheal suctioning are commonly performed procedures to prevent these complications. Due to the increased risk of pulmonary complications during prolonged ventilation in TBI patients, tracheostomy is recommended in order to reduce the number of mechanical ventilation days and the incidence of ventilator-associated pneumonia, when the benefits outweigh the risk of complications from tracheostomy.<sup>[20]</sup> However, there is no



**Figure 3.** (A) Percentage of patients requiring rescue propofol, and mean propofol dosage used during the study. (B) Percentage of patients requiring rescue fentanyl, and mean fentanyl dosage used during the study. <sup>\*</sup>P < .05 vs Group S, <sup>^</sup>P < .05 vs Group D1, <sup>&</sup>P < .05 vs Group D2.

**Table 3**  
**Adverse events of 3 groups during surgery.**

| Variable               | Group S (n=66) | Group D1 (n=62) | Group D2 (n=68) | P values |
|------------------------|----------------|-----------------|-----------------|----------|
| Hypertension           | 15 (22.73%)    | 14 (22.58%)     | 8 (11.76%)*,†   | .173     |
| Tachycardia            | 18 (27.27%)    | 15 (24.19%)     | 9 (13.24%)*,†   | .117     |
| Hypotension            | 7 (10.61%)     | 8 (12.90%)      | 11 (16.18%)     | .651     |
| Bradycardia            | 6 (9.09%)      | 7 (11.29%)      | 9 (13.24%)      | .782     |
| Coughing               | 51 (77.27%)    | 45 (72.58%)     | 43 (63.24%)     | .189     |
| Respiratory depression | 5 (7.58%)      | 3 (4.84%)       | 1 (1.47%)*,†    | .220     |

Variables presented as number of patients n (%).

\*  $P < .05$  vs Group S.†  $P < .05$  vs Group D1.

evidence to confirm that early tracheostomy reduces the mortality rate among TBI patients.

Previous research showed that tracheal intubation leads to an average increase in blood pressure by 40% to 50% and an average increase in HR of 20%, which is mainly due to the excitation of the sympathetic nervous system caused by stimulation of the upper respiratory tract.<sup>[21]</sup> Post-stress sympathetic activity is one of the body's important protective responses. However, sympathetic overactivity, such as PSH, can increase secondary brain injury, which seriously affects prognosis. It has been reported that 7.7% to 33% of TBI patients in NICUs experience PSH even without percutaneous tracheostomy.<sup>[22]</sup> Baguley et al proposed a PSH diagnostic system, the PSH Assessment Measure (PSH-AM), that enables doctors to diagnose PSH more precisely; it assesses the probability of the PSH diagnosis as “unlikely”, “possible”, or “probable”, and also assesses the severity of the clinical features.<sup>[23]</sup> Currently, beta-blockers, opioids, bromocriptine, and baclofen are the commonly used drugs to successfully alleviate PSH episodes.<sup>[24]</sup> Previous research on TBI patients treated with either DEX or propofol/midazolam found no significant between-group differences regarding the proportions of patients who met the “probable” or “possible” criteria, but more patients met the “unlikely” criteria in the DEX group compared to the propofol/midazolam group.<sup>[25]</sup> There have been no studies comparing the effect of DEX vs sufentanil on the alleviation of PSH episodes in TBI patients.

Previous research among TBI patients confirmed that SBP  $\geq 100$  mmHg for patients aged 50 to 69 years, or  $\geq 110$  mmHg for patients aged 15 to 49 or  $\geq 70$  years, may be associated with decreased mortality and improved outcomes.<sup>[26]</sup> As a result, we defined hypertension (MAP  $> 110$  mmHg or SBP  $> 160$  mmHg) and hypotension (MAP  $< 70$  mmHg or SBP  $< 110$  mg) in this study. We only included TBI patients aged 40 to 65 years with severe craniocerebral injury (GCS  $< 8$ ) because previous research showed that age and initial GCS are closely related to TBI-related

hospitalization and death.<sup>[26]</sup> We did not use steroids in this trial because a previous study reported that methylprednisolone was associated with increased mortality, and it is contraindicated for animals with severe TBI.<sup>[27]</sup>

Sedative agents and opioids are commonly used for the management of critically ill patients with TBI in NICUs. Additionally, benzodiazepines have been the first-line treatment for agitation among TBI patients for many years because of their efficacy in decreasing the incidence of seizures. However, these drugs, which act on the gamma-aminobutyric acid (GABA) system, can significantly suppress respiratory function and eventually cause hypercarbia, hypoxemia, and hypotension.<sup>[28,29]</sup>

DEX exerts neuroprotective effects by activating  $\alpha 2A$  receptors, while its activation of  $\alpha 2B$  receptors constricts cerebral vessels and decreases cerebral blood flow (CBF). As a result, the potential benefits of DEX for TBI patients need to be weighed against the potential adverse effects on both systemic hemodynamics and CBF.<sup>[30]</sup> A previous study reported that, when blood pressure of TBI patients was maintained at the pre-sedation level, there were no significant changes in CBF, cerebral metabolic rate equivalent (CMRe), or the CMRe/CBF ratio induced by DEX (before vs after DEX).<sup>[31]</sup> The authors also found that the percentage of CBF reduction was greater in patients without TBI than in the TBI patients.<sup>[31]</sup> The neuroprotective effect of DEX may involve many aspects, such as the suppression of circulating catecholamine concentrations, promotion of oxidative metabolism in astrocytes, reduction of available glutamine, and modulation of the balance between pro- and anti-apoptotic proteins.

However, one of the biggest problems of DEX is its cost.<sup>[32,33]</sup> A previous study reported that the average cost of DEX was \$32.49, while the average cost of 1% lidocaine with epinephrine during awake tracheotomy was only \$2.00. However, the latter cases required 2.4 times the dose of narcotics compared to the former cases during surgery. Additionally, compared with the overall cost of a tracheotomy procedure (\$1997–2072), only

**Table 4**  
**Comparison of coughing grade among the 3 groups.**

| Variable | Group S (n=66) | Group D1 (n=62) | Group D2 (n=68) | P values |
|----------|----------------|-----------------|-----------------|----------|
| Grade 1  | 15 (22.73%)    | 17 (27.42%)     | 25 (36.76%)     | .189     |
| Grade 2  | 28 (42.42%)    | 23 (37.10%)     | 24 (35.29%)     | .690     |
| Grade 3  | 10 (15.15%)    | 11 (17.74%)     | 10 (14.71%)     | .911     |
| Grade 4  | 5 (7.58%)      | 4 (6.45%)       | 6 (8.82%)       | .944     |
| Grade 5  | 8 (12.12%)     | 7 (11.29%)      | 3 (4.41%)       | .212     |

The variables are presented as number of patients, n (%).

1.6% and 0.10% of the total cost are accounted for by medication.<sup>[34]</sup>

Both thiopental and barbiturate have been found to have beneficial effects on CBF and the cerebral metabolic rate of oxygen (CMRO<sub>2</sub>). However, it is noteworthy that the 2 drugs can cause hypotension which can decrease the cerebral perfusion pressure.<sup>[35]</sup> Propofol, which inhibits the N-methyl-D-aspartate subtype of glutamate receptors and has agonistic activity at GABA receptors, has been used in TBI patients because it has been demonstrated to reduce CBF, CMRO<sub>2</sub>, and intracranial pressure in many studies. However, it has failed to show improvement in the 6-month mortality rate among TBI patients.<sup>[36]</sup> Caution is also required as high-dose propofol can lead to many complications such as respiratory depression, propofol-related infusion syndrome, infection, and increased serum amylase and lipase concentrations.<sup>[37]</sup> Although there are no strong and definitive recommendations for the use of lidocaine, previous research showed that intravenous lidocaine blunted the cough reflex both by blocking fast voltage-gated Na<sup>+</sup> channels via neuronal blockade of vagal reflex pathways and by a direct effect on the smooth muscle cells of the respiratory pathway.<sup>[38]</sup>

The ideal anesthesia state during percutaneous tracheostomy is effective sedation without hypoxemia or movement. The elimination half-time of sufentanil, DEX, and propofol are 13, 2 to 3, and 0.8 hours, respectively. DEX can potentiate the effects of anesthetic agents, which may explain the exaggerated respiratory depression when it is combined with propofol, midazolam, or opioids. The most common adverse reactions to DEX are hypotension (30%) and bradycardia (9%).<sup>[11]</sup> However, we did not observe any significant differences among the 3 groups during surgery with respect to bradycardia or hypotension. One case report found that DEX in conjunction with narcotics provided adequate sedation to complete percutaneous tracheostomy without inhibiting the patient's protective airway reflexes or respiratory drive.<sup>[39]</sup> A previous study reported that there were no irregular or apneic periods in respiratory function at an infusion rate of up to 1.5 μg·kg<sup>-1</sup>·hour<sup>-1</sup> DEX.<sup>[40]</sup> However, to minimize the adverse effects in the current study, both the bolus and continuous infusion doses of DEX were still within the manufacturer's recommended doses. Besides DEX, other agents have been previously used for procedural sedation during percutaneous tracheostomy, such as benzodiazepines and propofol, which can induce significant respiratory depression and loss of protective airway reflexes.<sup>[6,9]</sup> Additionally, a previous study reported that DEX may be used as an adjunctive treatment for refractory intracranial hypertension in NICUs without compromising hemodynamics, which may also apply during percutaneous tracheostomy.<sup>[41]</sup> Though previous study has reported the efficacy of dexmedetomidine-remifentanyl in children undergoing flexible bronchoscopy, we compared sufentanil vs dexmedetomidine in this study for the patients of different ages.<sup>[42]</sup> Sufentanil has also considerable side effects, including nausea, vomiting, urinary retention, and respiratory depression.<sup>[43]</sup> In order to reduce the consumption of sufentanil, incision sites were injected with 1% lidocaine with epinephrine at a ratio of 1:100,000 in our study. As a result, compared with previous study, the incidence of respiratory depression (7.58% vs 4.84% vs 1.47% in groups S, D1, and D2, respectively, *P* = .013, Table 3) was reduced in our study.<sup>[44]</sup>

Although therapeutic hypothermia (TH) and targeted temperature management (TTM) have been successfully used in a number of individual institutions to treat TBI, subarachnoid

hemorrhage and spinal cord injury, larger multicenter randomized trials have failed to demonstrate the benefits of TH and TTM compared to normothermia. There are likely many underlying reasons, among which the level of hypothermia, cooling duration, rewarming rate, and patient gender are considered to be the critical factors.<sup>[45]</sup> Additionally, hypothermia is associated with many adverse events, such as coagulopathy, immunosuppression, and cardiac dysrhythmia.<sup>[46]</sup> Furthermore, posttraumatic hyperthermia should be avoided to reduce vascular permeability, edema formation, and inflammatory cell infiltration into the injured brain regions, which all occur to greater degrees during hyperthermia compared with normothermia.<sup>[47]</sup> As a result, we used a forced-air warming device to maintain normothermia during surgery.

There are several limitations in this study. First, this study is a prospective, single-center, relatively small controlled trial, and a multicenter prospective controlled trial is necessary to verify the results. Second, TH or TTM combined with neuroprotective drugs may have additive or synergistic effects for TBI patients and the optimal titration of DEX is also unknown and is worthy of further study. Third, we did not record the blood gas analysis, PaO<sub>2</sub>, PaCO<sub>2</sub>, pH and continuous CO<sub>2</sub> concentration prior to and during sedation for the economic reasons. Finally, we did not objectively assess the degree of TBI based on circulating biomarkers (due to the lack of specific circulating biomarkers) or via noninvasive/invasive strategies (such as, monitoring the partial pressure of brain tissue oxygen [PbtO<sub>2</sub>] or brain tissue microdialysis).<sup>[48]</sup>

In brief, this trial demonstrated that DEX can be safely and effectively used in TBI patients during percutaneous tracheostomy. It decreased the number of intraoperative patient movements, rescue doses of propofol and fentanyl, and incidences of tachycardia, hypertension, and respiratory depression. However, larger, multicenter, randomized controlled trials are needed to verify the role of DEX in the management of TBI patients.

## Author contributions

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