# Effect of Dexmedetomidine Combined with Remifentanil on Emergence Agitation During Awakening from Sevoflurane Anesthesia for Pediatric Liver Surgery

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: We aimed to assess the effect of dexmedetomidine (Dex) combined with remifentanil on emergence agitation (EA) during awakening from sevoflurane anesthesia for pediatric liver surgery.

Material/Methods: Sixty children who underwent liver surgery in our hospital were prospectively selected and randomly allocated into group A (placebo+remifentanil+sevoflurane) or group B (Dex+remifentanil+sevoflurane). Mean arterial pressure (MAP) and heart rate (HR) at different time points, agitation score during awakening, behavioral status, pain level, and the incidence of postoperative adverse effects were compared in both groups.

Results: Children in group B had lower HR and MAP levels immediately after tracheal extubation and 5 min after tracheal extubation than those in group A. The Aono's scores, PAED agitation scores, and CHIPP scores at 15 min and 30 min of admission to the PACU were lower in group B than in group A. The incidence of agitation during postoperative anesthesia awakening was lower in group B in contrast to group A. There was no significant difference in postoperative adverse reactions between group A and group B.

Conclusions: In pediatric liver surgery, the use of Dex+remifentanil+sevoflurane anesthesia can reduce the incidence of EA during the awakening period, stabilize hemodynamic levels, and relieve postoperative pain, and has fewer postoperative adverse effects, which warrants clinical application.

Keywords: Dexmedetomidine • Remifentanil

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## Introduction

Inhalational anesthesia induction is a method commonly used by pediatric anesthesiologists. This is a pivotal technique in such cases due to the lack of venous access and possible airway difficulties [1]. Sevoflurane is broadly applied in pediatric anesthesia for its quick action, hemodynamic stability, low hepatotoxicity, relative lack of airway irritation, and rapid emergence from anesthesia. However, sevoflurane anesthesia in children correlates with a higher prevalence of emergence agitation (EA) [2]. EA is a self-limited condition of psychomotor excitement in the process of awakening from general anesthesia, which is limited to the emergence period when consciousness recovery sharply differs from other psychiatric states after surgery [3]. The chief clinical manifestations of EA in children include moaning, wiggling, crying, restlessness, incoherent speech, and disorientation, as well as inability to be comforted and to recognize people or objects [4,5]. Therefore, it is imperative to select suitable and targeted medicines according to the personal condition of the patient to better prevent the occurrence of EA.

Several types of drugs are applied for preventing EA from sevoflurane anesthesia in children, such as the use of opioids, benzodiazepines, α2 agonists, intravenous anesthetics, non-opioid analgesics, and short-acting midazolam [6]. Dexmedetomidine (Dex) is defined as a highly selective α2-adrenoceptor agonist, which uniquely retains respiratory drive, generates arousable sedation, and decreases the incidence and duration of delirium after surgery [7,8]. Dex produces both sympatholytic and dose-dependent analgesic and sedative effects, and weakens neuroendocrine and hemodynamic responses associated with surgery and anesthesia [9]. Evidence has shown that Dex significantly decreases the incidence of EA of pediatric patients after ophthalmologic surgery under sevoflurane anesthesia [10]. Remifentanil is a potent opioid with strong, ultra-short action and fast action rate, which is used by anesthesiologists as an adjunct to total intravenous anesthesia because of its ease of dose adjustment, rapid offset, and synergistic effects with propofol [11]. Additionally, remifentanil has been utilized as an adjuvant to general anesthesia because of its analgesic influence diminishing intraoperative analgesia, its intraoperative

antihypertensive effect, and subsequent reduction of intraoperative blood loss [12,13]. Moreover, remifentanil used as an adjuvant to sevoflurane does not cause acute opioid tolerance or hyperalgesia [14]. In recent years, with the advances in surgical techniques and technology, and better recognition of the underlying physiology, anesthesia for hepatic resection has changed considerably [15]. The clinical use of these drugs has recently been revealed to reduce EA following sevoflurane anesthesia, but it has adverse effects of postoperative vomiting, respiratory depression, and opioid-evoked hyperalgesia [16]. In the present study, we assessed the effect of Dex combined with remifentanil on EA during awakening from sevoflurane anesthesia for pediatric liver surgery.

## Material and methods

### Ethics Statement

The study was approved by the Medical Ethics Committee of our hospital (approval number: 20201029), and patients and their families were informed of the study and signed consent forms.

### General Data

Sixty children who underwent liver surgery in our hospital were recruited in this prospective study and were randomly allocated into group A and group B using a computer-generated random number list (n=30 cases). The general data on age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) grading, and type of liver mass between the 2 groups of children showed no significant differences between groups (*P*>0.05; **Table 1**) and were comparable.

Inclusion criteria were age 1-6 years, ASA grade I or II, need to perform surgical removal of liver masses, and met relevant surgical indications.

Exclusion criteria were upper respiratory tract infection within the past 3 weeks; cognitive developmental abnormalities or dysplasia, contraindications to the medications used,

**Table 1.** Comparison of general data in the 2 group.

| | Group A (n=30) | Group B (n=30) | *P* value |
|---|---|---|---|
| Gender (Male/Female) | 20/10 | 17/13 | 0.426 |
| Age (years) | 4.07±1.31 | 3.93±1.28 | 0.692 |
| Body mass index (kg) | 16.57±4.16 | 15.98±4.24 | 0.588 |
| ASA grading (I/II) | 26/4 | 22/8 | 0.197 |
| Type of mass (benign tumor/malignant tumor/other) | 9/15/6 | 10/17/3 | 0.555 |

respiratory diseases, associated disorders that cause agitation such as epileptic seizures and schizophrenia, cardiac or renal dysfunction, and incomplete clinical data.

## Anesthesia and Intervention

### Preparation for anesthesia

Children in both groups were routinely fasted for 6 h and liquid-fasted for 2 h before the operation. All children had a venous access established before admission to the operating room and were continuously dripped with glucose solution (Hengrui Pharmaceuticals, Jiangsu, China). Heart rate (HR), blood oxygen saturation ($SpO_2$), electrocardiogram (ECG), and electroencephalographic bispectral index (BIS) were routinely monitored.

### Induction of anesthesia

At the end of monitoring, the child inhaled 8% sevoflurane (Baxter Healthcare Corporation, Guayama, Puerto Rico, USA) through a mask, and was injected intravenously with 2 μg/kg fentanyl citrate (Yichang Humanwell Pharmaceutical, Hubei, China) and 0.1 mg/kg cisatracurium (Hengrui Pharmaceuticals). After loss of consciousness, the child was ventilated with oxygen denaturation through a mask with pressurized ventilation, and endotracheal intubation was performed. The anesthesia machine was connected, mechanical ventilation was used, and respiratory parameters were adjusted to oxygen flow (2 L/min), tidal volume (Vt) (6-8 mL/kg), respiratory ratio (1: 1.5), respiratory rate (15-20 breaths/min), and partial pressure of end-tidal carbon dioxide ($PETCO_2$: 35-40 mmHg).

### Intraoperative maintenance

After correctly connecting all the monitoring equipment, children in group B were first injected intravenously with a 1 μg/kg loading dose of dexmedetomidine hydrochloride (Sichuan Guorui Pharmaceutical Co., Ltd., Sichuan, China), and then dexmedetomidine was continuously pumped at a rate of 0.2-0.4 μg/kg·h. In group A, saline was continuously pumped intravenously in an equal volume. Then, the child was maintained under anesthesia with intraoperative inhalation of 2% sevoflurane and intravenous infusion of 0.2 μg/kg/mim remifentanil hydrochloride (Yichang Humanwell Pharmaceutical). The child's hemodynamic stability was maintained, blood pressure and HR were maintained within the basal values of ±20%, and BIS values were maintained at 40-60. An intraoperative warming blanket was used, and the body temperature was maintained at 36.0-37.5°C.

### Postoperative awakening

At the end of the operation, drug administration was stopped and the children in both groups were admitted to the post-anesthesia care unit (PACU). When the child resumed spontaneous and regular respiration, tidal volume was >6 ml/kg, and $SpO_2$ was ≥95% and lasted for >1 min, the endotracheal tube was removed after suctioning the oral and airway secretions.

## Observational Indicators

MAP and HR were recorded before induction of anesthesia (T0), immediately after tracheal intubation (T1), at the end of surgery (T2), immediately after tracheal extubation (T3), and 5 min after tracheal extubation (T4) in the 2 groups of children.

Sedation, agitation, and pain level were assessed using Aono's score [17], Craner's Pediatric Anesthesia Emergence Delirium (PAED) [18], and Children's and Infants' Postoperative Pain Scale (CHIPPS) [19] for children in both groups at 0 min, 15 min, and 30 min of admission to the PACU, respectively. (1) Aono's score was employed to evaluate the child's behavioral state: 1 for quiet; 2 for not quiet, but comforting; 3 for not quiet, moderately agitated, or disturbed; and 4 for belligerent, excitable, or disoriented. (2) The PAED scored the degree of agitation on a 5-item scale that included obeying commands and being communicative, behavior being purposeful, attention to changes in the surroundings, inability to be soothed by crying, and inability to be comforted. Each item was divided into 5 grades, of which the first 3 indicators were scored once: none (4 points), poor (3 points), moderate (2 points), good (1 point), and very good (0 point). The latter 2 indicators were scored in the following order: none (0 point), mild (1 point), moderate (2 points), severe (3 points), and very severe (4 points). The sum of the scores was taken as the PAED score, with higher scores representing more severe agitation during the awakening period. (3) The CHIPPS score examined the pain level and was based on 5 dimensions: crying, facial expression, trunk posture, lower limb posture, and restlessness, with a range of 0-2 points for each item and a total score of 10 points. Higher scores represented higher pain levels.

The general surgical conditions of the children in both groups were recorded, including the surgery time, extubation time, awakening time, and PACU retention time.

The incidence of awakening agitation (Aono's score ≥4 and total score >12 on the PAED scale) and adverse effects (respiratory depression, nausea, and vomiting) were recorded in both groups.

## Statistical Methods

Data analysis was conducted with SPSS 26.0 software (IBM SPSS Statistics, Chicago, IL, USA). The homogeneity of variance and

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**Table 2.** Comparison of the general conditions of children in the 2 groups.

| | Group A (n=30) | Group B (n=30) | P value |
|---|---|---|---|
| Time of surgery (min) | 148.27±27.49 | 153.05±31.86 | 0.541 |
| Extubation time (min) | 8.75±2.28 | 9.23±2.72 | 0.549 |
| Time of awakening (min) | 12.30±3.06 | 13.13±3.28 | 0.315 |
| PACU retention time (min) | 44.40±7.35 | 46.17±7.82 | 0.370 |

**Table 3.** Comparison of MAP and HR at different time points in the 2 groups.

| Group | Time | HR (times/min) | MAP (mmHg) |
|---|---|---|---|
| Group A (n=30) | T0 | 70.25±7.83 | 86.30±9.69 |
| | T1 | 89.10±8.81* | 93.01±8.63* |
| | T2 | 80.31±8.06* | 88.86±9.24 |
| | T3 | 96.34±9.11* | 95.31±8.17* |
| | T4 | 83.50±8.45* | 87.14±8.99 |
| Group B (n=30) | T0 | 71.44±7.67 | 85.52±9.05 |
| | T1 | 88.37±8.01* | 94.20±8.51* |
| | T2 | 79.69±7.61* | 84.58±7.41 |
| | T3 | 91.24±8.07*# | 90.39±8.05*# |
| | T4 | 79.42±7.47*# | 82.65±7.96# |

* $P<0.05$ vs T0 time point; # $P<0.05$ vs Group A.

normal distribution were confirmed by Levene and Kolmogorov-Smirnov (K-S) tests. Measurement data were represented by mean±standard deviation and compared by $t$ test. Enumeration data were represented by number of cases or percentage (%) and were assessed by $\chi^2$ test. $P<0.05$ indicated a statistically significant difference.

## Results

### General Surgical Conditions of the Children

No significant difference was noted in the surgery time, extubation time, awakening time, and PACU retention time of children in the 2 groups ($P>0.05$, **Table 2**).

### MAP and HR at Different Time Points

At T0, there was no significant difference in HR and MAP levels between the 2 groups ($P>0.05$); HR was higher than T0 in both groups from T1 to T4 time points; MAP levels were higher than T0 time point in both groups at T1 and T3 time points; and children in group B had significantly lower HR and MAP levels at T3 and T4 time points than those in group A ($P<0.05$, **Table 3**).

### Aono's Score and PAED Agitation Score at Different Time Points

Aono's scores and PAED agitation scores were lower at 15 min into the PACU, at 30 min into the PACU compared to entry into the PACU in both groups; the Aono's scores and PAED agitation scores at 15 min and 30 min of admission to the PACU were lower in children in group B than in group A ($P<0.05$) (**Table 4**).

### CHIPP Scores at Different Time Points

Compared with the time of admission to the PACU, the CHIPP scores were reduced in both groups at 15 min and 30 min of admission to the PACU, and the CHIPP scores were lower in group B than in group A at 15 min and 30 min of admission to the PACU ($P<0.05$, **Table 5**).

### Incidence of Agitation and Adverse Reactions During Awakening

The incidence of agitation during postoperative anesthesia awakening was lower in children in group B in contrast to group A ($P<0.05$). There was no significant difference in postoperative adverse reactions between group A and group B ($P>0.05$) (**Table 6**).

**Table 4.** Comparison of Aono's score and PAED agitation score at different time points between the 2 groups of children.

| Group | Time | Aono's score | PAED agitation score |
|---|---|---|---|
| Group A (n=30) | Entry into the PACU | 2.79±0.77 | 11.69±1.14 |
| | At 15 min into the PACU | 2.00±0.73* | 8.78±0.96* |
| | At 30 min into the PACU | 1.76±0.54* | 4.10±0.43* |
| Group B (n=30) | Entry into the PACU | 2.71±0.69 | 11.14±1.07 |
| | At 15 min into the PACU | 1.58±0.57*# | 7.12±0.80*# |
| | At 30 min into the PACU | 1.43±0.51*# | 3.69±0.36*# |

* $P<0.05$ vs entry into the PACU; # $P<0.05$ vs Group A.

**Table 5.** Comparison of postoperative pain levels between the 2 groups of children.

| CHIPP scores | Group A (n=30) | Group B (n=30) |
|---|---|---|
| Entry into the PACU | 5.58±1.24 | 5.43±1.10 |
| At 15 min into the PACU | 3.31±0.95* | 2.62±0.81*# |
| At 30 min into the PACU | 2.13±0.69* | 1.66±0.67*# |

* $P<0.05$ vs entry into the PACU; # $P<0.05$ vs Group A.

**Table 6.** Comparison of the incidence of agitation and adverse reactions during awakening in 2 groups of children.

| Item | Group A (n=30) | Group B (n=30) | P value |
|---|---|---|---|
| Incidence of agitation | 8 (26.67) | 1 (3.33) | 0.038 |
| Adverse reactions | | | |
| Respiratory depression | 1 (3.33) | 0 (0.00) | |
| Nausea | 2 (6.67) | 0 (0.00) | |
| Vomiting | 3 (10.00) | 2 (6.67) | |
| Total adverse reaction rate | 6 (20.00) | 2 (6.67) | 0.129 |

## Discussion

EA is an undesirable postoperative complication that can occur in patients at any age, but most commonly in children [20]. Effective EA preventive approaches consist of elimination of correctable risk factors, identification of risk factors, and application of pharmacological and non-pharmacological therapies [21]. Emergence delirium (ED) is a severe subtype of EA, which is a state of consciousness. Usually, EA and ED are used interchangeably [22]. Anesthetic adjuvants such as ketamine, remifentanil, propofol, fentanyl, and other drugs have been applied for preventing EA, but these drugs can increase sedation after anesthesia, causing slow awakening and some adverse effects [23].

In our study, 60 children who underwent liver surgery were allocated into group A (treated with placebo+remifentanil+sevoflurane) or group B (treated with Dex+remifentanil+sevoflurane). MAP and HR were recorded, sedation, agitation, and CHIPPS scores were assessed, the general surgical conditions were recorded, and the incidence of awakening agitation and adverse effects were recorded in both groups. The PAED scale is widely applied to assess ED in children after surgery or diagnostic procedures [24]. Postoperative pain must be considered when assessing ED. Dex administration can be accompanied by a reduction in HR and blood pressure [25]. We found that Dex combined with remifentanil significantly relieves EA during awakening from sevoflurane anesthesia for pediatric liver surgery, improves hemodynamic levels and postoperative pain, and has fewer adverse effects.

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Dex has been reported to diminish the risk of ED and EA in pediatric patients [26]. The clinical effect of titration of Dex doses is particularly crucial after liver transplantation in children because the weight-based administration may be poorly correlated with plasma concentrations [27]. Intraoperative low-dose Dex administration is associated with reduced incidence of moderate-to-severe hepatic ischemia-reperfusion injury in pediatric deceased liver transplantation [28]. Specifically, Dex can restrain the sympathetic nerve activity, thereby decreasing blood pressure and HR, maintaining hemodynamic stability during anesthesia, and possessing the functions of analgesia, sedation, anti-anxiety, and suppression of sympathetic nerve excitement [23,29]. A meta-analysis found that Dex reduces the incidence of ED in children under sevoflurane anesthesia, and its use reduces postoperative pain, thus diminishing the adverse effects of opioid administration [30]. Shi et al reported that Dex administration can decrease the ED incidence post-tonsillectomy under sevoflurane anesthesia and can be utilized to safely avoid postoperative behavior changes [31]. These articles validate the positive functions of Dex in mitigating EA. Remifentanil has multiple additional clinical benefits, such as rapid onset, lack of accumulation, and very short context-sensitive half-time [32,33]. Continuous intraoperative infusion of remifentanil effectively decreases EA incidence without clinically marked hemodynamic deterioration or delayed recovery time in children receiving ophthalmic surgery under sevoflurane anesthesia [34]. Choi et al have also supported that remifentanil reduces EA in children aged 3-9 years undergoing strabismus surgery under sevoflurane anesthesia [34]. These articles verify the positive functions of remifentanil in mitigating EA.

Moreover, our study highlighted the combined effect of Dex and remifentanil in EA during awakening from sevoflurane anesthesia for pediatric liver surgery. As previously reported, target-controlled infusion of remifentanil and a single dose of Dex can reduce hemodynamic stimulation and airway response during recovery from anesthesia [35]. For gastric sleeve bariatric surgery patients, the intraoperative use of Dex or remifentanil as adjuvant to general anesthesia is a suitable way to achieve hemodynamic control and improve perioperative outcomes [36]. Furthermore, combined administration of remifentanil with Dex under sevoflurane anesthesia has acceptable oxygenation, cardiovascular effects, and acid-base balance, and does not impede renal function [37]. These studies all agree with our results.

## Conclusions

In conclusion, we found that, in pediatric liver surgery, the use of Dex+remifentanil+sevoflurane anesthesia can reduce the incidence of EA during the awakening period, stabilize hemodynamic levels, and relieve postoperative pain, and has fewer postoperative adverse effects, and it warrants clinical application. This study provides some guidelines for the clinical mitigation of EA during awakening from sevoflurane anesthesia for pediatric liver surgery. However, we did not calculate the sample size, which is a limitation of this study, and studies with larger samples are needed to verify our findings.

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