BMJ Paediatrics Open

# Comparing different administration methods of subanaesthetic propofol to mitigate emergence agitation in preschool children undergoing day surgery: a double-blind, randomised controlled study

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**To cite:** Chen J, Shi X, Hu W, *et al*. Comparing different administration methods of subanaesthetic propofol to mitigate emergence agitation in preschool children undergoing day surgery: a double-blind, randomised controlled study. *BMJ Paediatrics Open* 2025;**9**:e002376. doi:10.1136/bmjpo-2023-002376

Received 4 November 2023
Accepted 20 February 2025



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## ABSTRACT

**Background** Preschool children who received sevoflurane anaesthesia were associated with a high incidence of emergence agitation (EA). Studies have shown that a subanaesthetic dose of propofol (1 mg/kg) at the end of inhalational anaesthesia could reduce EA in paediatric patients, but the optimal administrations are still under investigation.

**Methods** In a double-blind trial, 160 preschool children (ASA I or II, 2–5 years old) undergoing day surgery of laparoscopic inguinal hernia repair with sevoflurane anaesthesia were randomly assigned into four groups: the control group, single bolus 3 min before the end of the surgery (bolus A), single bolus at the end of the surgery (bolus B) and continuous infusion for 3 min at the end of the surgery (continuous infusion). The dose of propofol in the bolus A group, bolus B group and continued infusion group is 1 mg/kg. The primary outcomes were the incidence and severity of EA assessed by the Paediatric Anaesthesia Emergence Delirium (PAED) scale and Watcha scales. The secondary outcomes included extubation time, emergence time, mean arterial pressure and heart rate.

**Results** The incidence of EA was as follows: 65.0% in the control group, 30.0% in the bolus A group, 32.5% in the bolus B group and 5.0% in the continuous infusion group ($p<0.05$). Furthermore, the peak PAED scores in the continuous infusion group were significantly lower than those in the other groups. However, extubation time and emergence time showed no differences among groups.

**Conclusions** Continuous infusion of subanaesthetic dose propofol (1 mg/kg) for 3 min at the end of sevoflurane anaesthesia seems to be more appropriate than other administration as it reduced EA and did not prolong the time to wake.

**Trail registration number** NCT05420402.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Emergence agitation is commonly observed in preschool children and causes many adverse effects.
⇒ Subanaesthetic dose propofol could reduce emergence agitation following sevoflurane anaesthesia in paediatric patients.

### WHAT THIS STUDY ADDS

⇒ Comparing to a single bolus, continuous infusion for 3 min of subanaesthetic dose propofol could reduce the incidence and severity of emergence agitation more effectively.
⇒ It also adds to the comprehension about the mechanism of propofol reducing emergence agitation.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Provides a new clinical strategy for anaesthesiologists to manage emergence agitation in paediatric patients, improving the quality of anaesthesia.
⇒ By improving the emergence quality of paediatric patients, accelerating the efficiency of day surgery and improving the safety and comfort of day surgery.

## INTRODUCTION

Emergence agitation (EA) is a prevalent occurrence following sevoflurane anaesthesia, with an incidence of up to 80%, particularly among preschool children.[1 2] EA is characterised as a 'dissociated state of consciousness' in which the child displays irritability, uncooperativeness, incoherence, and inconsolable crying, moaning, kicking, or thrashing behaviour.[3] Furthermore, EA in children can potentially be dangerous as it may lead to incidents such as falling out of bed and removal of surgical dressings and intravenous catheters.[4]

Several pharmacological prophylactic interventions, including propofol, have demonstrated the potential to reduce the incidence of EA following sevoflurane anaesthesia.[4–6] A small number of studies have shown that the effectiveness of a subanaesthetic dose

of propofol (1 mg/kg) bolus at the end of sevoflurane anaesthesia in reducing EA.[7–9] An infusion of 3 mg/kg of propofol over 3 min following sevoflurane anaesthesia has also been employed as a strategy to reduce EA, but it will prolong the emergence time.[10 11]

Despite these findings, there remains a significant gap in the literature regarding the optimal administration method of propofol to balance the reduction of EA and minimising prolonged emergence time. Most existing studies have focused on single administration methods without comparing multiple strategies directly within a single cohort of patients. Laparoscopic inguinal hernia repair (LIHR) in paediatric patients is a common day surgery procedure, offering several advantages such as convenience, lower cost and faster recovery.[12] Additionally, the specific population of preschool children undergoing LIHR, a group particularly susceptible to EA, has not been extensively studied in this context.

In this study, we aim to fill this gap by investigating the comparative effectiveness of different administrations of a subanaesthetic dose of propofol (1 mg/kg) in preventing EA among preschool children undergoing day surgery. Our findings may offer new guidance on the utilisation of propofol for the prevention of agitation in preschool children, thereby improving safety and comfort during day surgeries.

## METHODS

### Participants

From July 2022 to December 2022, a total of 160 children aged between 2 and 5 years old with an ASA (American Standards Association) physical status I or II, who would undergo day surgery of LIHR in Shenzhen Children's Hospital were randomly divided into 4 groups, with 40 cases in each group. The inclusion criteria were the children with normal results of auxiliary examinations before surgery, including blood routine, coagulation function, ECG and chest X-ray. The exclusion criteria were the children allergic to the drug used in the study, body mass index >25 kg/m$^2$, the children with neurological disorders, congenital heart disease, recent respiratory diseases or other important organ disease or duration of surgery more than 40 min.

### Patient and public involvement

Parents or the public were not directly involved in the design, conduct or plans for the dissemination of our research.

### Randomisation and double-blind

The trial used block randomisation to ensure equal distribution of participants across the groups. Block sizes were fixed at 8 and randomly changed to maintain unpredictability. SAS V.9.2 software was employed by statistical professionals to generate random sequences, ensuring methodological rigour. Each random number, along with its corresponding assignment, was placed in a sealed, opaque envelope. On recruitment, a field staff member, who was unaware of the study's hypotheses, opened these envelopes to assign participants to one of the four groups:

- Control group: No propofol treatment (received a volume-matched saline solution).
- Bolus A group: Intravenous bolus injection of 1 mg/kg propofol 3 min before the end of surgery.
- Bolus B group: Intravenous bolus injection of 1 mg/kg propofol at the end of surgery.
- Continuous infusion group: Continuous infusion of 1 mg/kg propofol for 3 min at the end of surgery.

This study employed a double-blind design. Both participants' caregivers and the clinical staff, including anaesthesiologists and outcome assessors, were blinded to the group assignments.

- Preparation of interventions: To prevent detection of group assignment due to the appearance of propofol, which is white, all syringes were wrapped in opaque coverings. An independent pharmacist, not involved in the study, prepared the syringes and ensured that both propofol and saline syringes were identical in terms of labelling, external appearance and volume.
- Administration of interventions: Anaesthesiologists, blinded to group assignment, administered the contents of the coded syringes based on instructions provided by the independent pharmacist. To ensure the appearance of consistent treatment across groups, infusion pumps were used in all groups. In the control group, a saline infusion was administered via the infusion pump for the same duration as the propofol infusion.
- Outcome assessment: Outcome assessors, who were blinded to the group assignments, recorded the incidence and severity of EA using the Paediatric Anaesthesia Emergence Delirium (PAED) scale and Watcha scales. They also recorded secondary outcomes such as extubation time, emergence time, mean arterial pressure (MAP) and heart rate (HR).

### Procedures

We routinely carried out health education for children and parents before surgery, explained the anaesthesia process and precautions, patiently answered their questions and guided parents or guardians to comfort their children before and after surgery. We recorded the children's demographic data: age, gender, weight, ASA grade, etc.

After entering the operating room, the children's HR, non-invasive blood pressure, pulse oximetry ($SpO_2$) and respiratory rate (RR) were continuously monitored. Anaesthesia induction was performed with 2.5 mg/kg propofol, 1 µg/kg remifentanil and 0.4 mg/kg rocuronium. After the anaesthetic drug took effect, a suitable laryngeal mask (LMA) was inserted. Anaesthesia was maintained by 2% sevoflurane and 0.2 µg/kg/min remifentanil to maintain the bispectral index monitor within the range of 40–60. The mechanical ventilation mode was volume-controlled ventilation. We adjusted

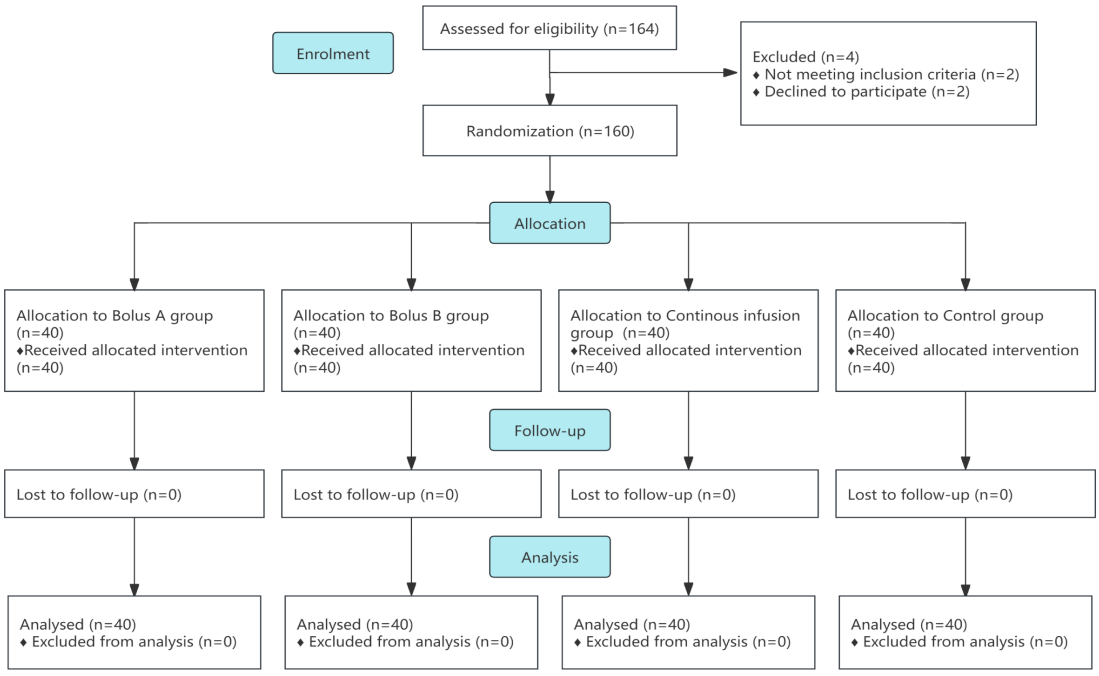


**Figure 1** Consolidated Standards of Reporting Trials flow diagram.

the tidal volume and the RR to maintain end-expiratory carbon dioxide partial pressure ($PetCO_2$) between 30 and 35 mm Hg. We discontinued the administration of sevoflurane and remifentanil 3 min prior to the conclusion of the procedure. Subsequently, we carried out the trial intervention in accordance with the assigned groups. The children in the control group received no treatment. The children in the bolus A group received an intravenous bolus injection of 1 mg/kg propofol 3 min before the end of the surgery. The children in the bolus B group received an intravenous bolus injection of 1 mg/kg propofol at the end of the surgery. The children in the continuous infusion group were subjected to a continuous infusion of 1 mg/kg propofol for 3 min at the end of the surgery. All the groups received local infiltration anaesthesia with 0.3% ropivacaine around the incision by the surgeon. The LMA was removed once tidal volumes exceeded 6 mL/kg, $SpO_2$ levels reached above 96% and $P_{ET}CO2$ remained below 50 mm Hg while breathing ambient air. All patients received oxygen through a face mask until emergence, and an oropharyngeal airway was inserted if airway obstruction was encountered.

## Measures

The primary outcome was the incidence and severity of EA according to the PAED[13] and Watcha scales,[14] recorded simultaneously at 5 min intervals until 30 min after emergence. The PAED scale consisted of five items: (1) the child makes eye contact with the caregiver, (2) the child shows purposeful actions, (3) the child is aware of his or her surroundings, (4) the child is restless and (5) the child is inconsolable. Items 1–3 are scored as follows: 4=not at all, 3=just a little, 2=quite a bit, 1=very much and 0=extremely. Items 4 and 5 are scored as follows: 0=not at all, 1=just a little, 2=quite a bit, 3=very much and 4=extremely. There existed four levels in the Watcha scale (1: calm or asleep; 2: crying and consolable; 3: crying and inconsolable and 4: severely agitated). EA on the PAED scale was defined as a PAED score >12 throughout the first 30 min after emergence. EA was diagnosed by a score of ≥3 on the Watcha scale at any point during the first 30 min after emergence.

The secondary outcomes included peak PAED scores, anaesthesia time, extubation time and emergence time.

**Table 1** Demographic characteristics of study participants (n=40)

| | Control | Bolus A | Bolus B | Continuous infusion |
|---|---|---|---|---|
| Age (year) | 3.55±1.31 | 3.18±1.13 | 3.03±1.10 | 3.20±1.20 |
| Weight (kg) | 16.79±3.55 | 15.28±3.40 | 15.95±4.25 | 16.36±3.99 |
| Gender (M/F) | 33/7 | 34/6 | 33/7 | 34/6 |
| Anaesthesia duration (min) | 28.48±3.64 | 27.82±2.69 | 28.38±3.61 | 29.15±2.66 |
| Extubation time (min) | 5.08±1.44 | 5.15±1.61 | 5.20±1.71 | 4.60±1.33 |

Values are presented as number of patient or mean±SD.
F, female; M, male.

Table 2 Comparison of emergence agitation, emergence time and incidence of adverse reactions among patients (n=40)

| | Control | Bolus A | Bolus B | Continuous infusion |
|---|---|---|---|---|
| Emergence agitation | | | | |
| Using the PAED scale | 26/40 (65.0%) | 12/40 (30.0%)* | 13/40 (32.5%)* | 2/40 (5.0%)*†‡ |
| Using the Watcha scale | 27/40 (67.5%) | 12/40 (30.0%)* | 1240 (30.0%)* | 2/40 (5.0%)*†‡ |
| Peak PAED scores | 13.5 (6, 16) | 7 (4, 13)* | 6 (5, 13)* | 4 (3, 6.75)*†‡ |
| Emergence time (min) | 13.46±2.77 | 13.72±4.18 | 14.59±4.35 | 14.60±3.63 |

Values are presented as number (%), median (IQR) or mean±SD.
*p<0.05, Significant difference compared with the control group.
†p<0.05, Significant difference compared with the bolus A.
‡p<0.05, Significant difference compared with the bolus B.
PAED, Paediatric Anaesthesia Emergence Delirium.

The anaesthesia time refers to the time from the beginning of anaesthesia to the emergence of children. The duration of extubation refers to the time between the end of the surgery and the removal of the LMA. The time to emergence was defined as the duration of time from the termination of anaesthesia until the onset of eye-opening or purposeful movement. The data of MAP, HR and $SpO_2$ were recorded after induction (T0), at the end of surgery (T1), after tracheal extubation (T2) and at the time of emergence (T3) were also recorded.

### Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows (V.26.0, IBM). Demographic data such as age, gender, weight, anaesthesia time, extubation time and emergence time, and peak PAED scores were carried out using the Mann-Whitney U test for non-normally distributed data and the analysis of variance for normally distributed data. The incidence of EA among the groups was analysed using a $\chi^2$ test with the Fisher's exact test correction compared in the time points. Haemodynamic variables in the same subjects were compared with the Bonferroni test after repeated measures of analysis of variance. P values <0.05 were considered to be statistically significant.

## RESULTS

A total of 164 children were enrolled in our study, and out of them, 4 children were excluded. Two patients were excluded: one due to surgery duration exceeding 40 min and the other due to asthma. Two patients declined to participate in the study. In total, 160 children finished this study, with 40 children in every group (figure 1). The demographic data such as the age, weight, gender, duration of anaesthesia and extubation showed no significant differences among the four groups (p>0.05) (table 1).

According to the PAED and Watcha scales, the incidence of EA in the bolus A group, the bolus B group and the continuous infusion group were significantly less than those in the control group (p<0.05). The incidence of EA in the continuous infusion was significantly less than the bolus A group and the bolus B group (p<0.05) (table 2). Peak PAED scores were also significantly lower in the continuous infusion group (median score=4) than in the bolus A group (median score=7), in the bolus B group (median score=6) and in the control group (median score=13.5) (p<0.05). However, there was no significant difference in the emergence time among all groups (p>0.05).

Figures 2 and 3 represent the percentage of children who experienced EA (PAED score >12, Watcha score ≥3) during the first 30 min after emergence. Comparing with

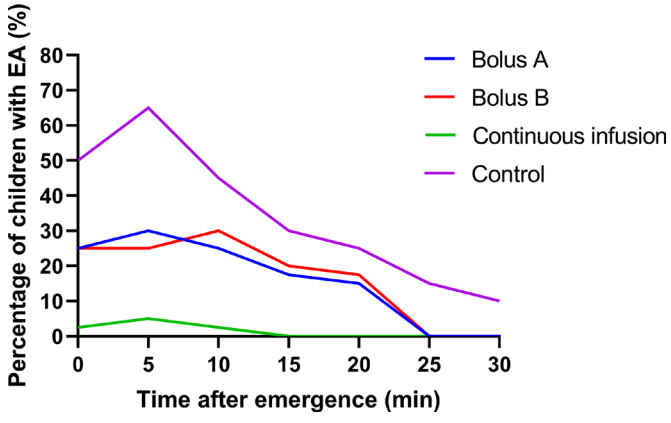


Figure 2 Proportion of patients with emergence agitation (EA) (PAED score >12) against time after emergence. PAED, Paediatric Anaesthesia Emergence Delirium.

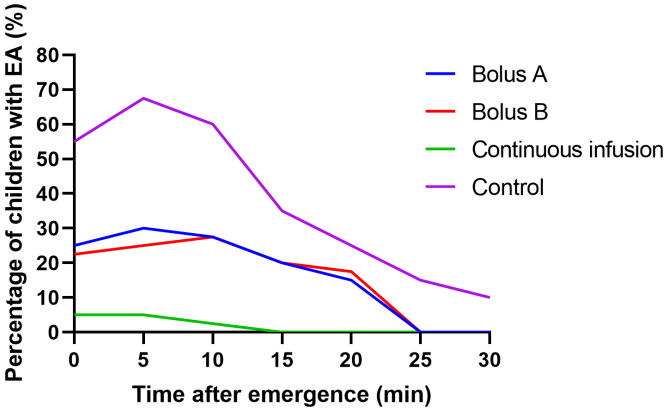


Figure 3 Proportion of patients with emergence agitation (EA) (Watcha score ≥3) against time after emergence.

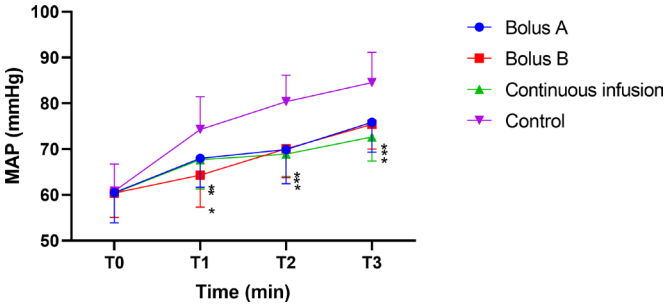


**Figure 4** A comparison of MAP at different time points. Significant difference compared with the control group. T0, after induction; T1, at the end of surgery; T2, after tracheal extubation; T3, at the time of emergence. *p<0.05. MAP, mean arterial pressure.

the control group, the percentage of patients with EA was significantly lower in the bolus A group, the bolus B group and the continuous infusion group. No patient in the continuous infusion group experienced EA beyond 15 min of emergence.

The period from induction to emergence, the HR and the MAP increased gradually. The HR and the MAP in the bolus A group, the bolus B group and the continuous infusion group were significantly less than in the control group at T1, T2 and T3 (p<0.05) (figures 4 and 5).

## DISCUSSION

In the present study, a subanaesthetic dose of propofol (1 mg/kg) at the end of sevoflurane anaesthesia could reduce EA. We observed an incidence of 65.0% of EA in the control group, 30.0% in the bolus A group, 32.5% in the bolus B group and 5.0% in the continuous infusion group. Continuous infusion of propofol 1 mg/kg for 3 min was associated with a significant decrease in the incidence, severity and duration of EA.

The aetiology of EA remains unclear and there are several risk factors that may be involved in its development, such as age, pain, different types of surgery, anaesthetic techniques and inhalation agents associated with rapid emergence.[4] Preschool children are the most susceptible group for EA. It may be related to the inability to adapt to a sudden switch to an unfamiliar

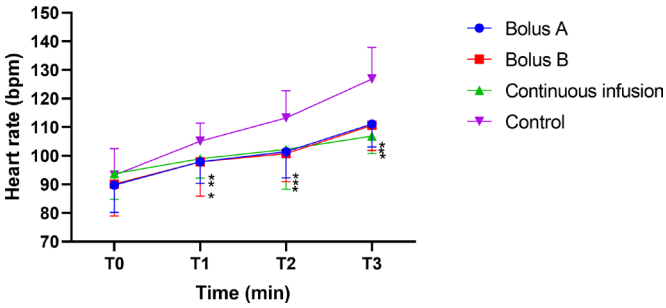


**Figure 5** A comparison of heart rate at different time points. Significant difference compared with the control group. T0, after induction; T1, at the end of surgery; T2, after tracheal extubation; T3, at the time of emergence. *p<0.05.

environment after awakening, immature neurological development, increased pain sensation and sympathetic hyperactivation.[15 16] Sevoflurane increases norepinephrine release in the preoptic area in the rat brain, which may cause disorientation in the early stages of recovery and lead to the occurrence of EA.[17] Additionally, elevated lactate and glucose concentrations in the parietal cortex due to sevoflurane anaesthesia have been proposed to induce EA.[18 19]

Propofol is known for its rapid onset and relatively short duration of action, which may act by enhancing the effect of gamma-aminobutyric acid (GABA), inhibiting N-methyl-D-aspartate (NMDA) receptors and modulating slow calcium ion channels.[20] Propofol allows for a smoother transition to consciousness as the sevoflurane wears off gradually.[11] This avoids abrupt awakening, which can be associated with increased agitation. According to its GABAergic effects and NMDA receptor modulation, propofol decreases neuronal activity and induces sedation, anxiolysis and amnesia during the emergence phase, minimising agitation.[21] Some clinical studies have shown that a bolus dose of 1 mg/kg of propofol was administered following sevoflurane anaesthesia to reduce the incidence of EA.[8 22 23] Abbas *et al*[11] and Costi *et al*[10] described that 3 mg/kg propofol administered over 3 min after cessation of sevoflurane anaesthesia was more effective in preventing EA, but the emergence time of patients was significantly prolonged.

Our study showed that continuous infusion of subanaesthetic dose of propofol for 3 min could emerge smoothly without delaying the emergence time. Dahmani *et al*[6] pointed out that the plasma concentration of propofol at emergence might affect the occurrence of EA. Compared with single bolus, continuous infusion of 1 mg/kg propofol for 3 min allows the drug concentration in the bloodstream to decline gradually, which may make plasma concentrations of propofol more likely to reach the level of preventing EA. The continuous infusion provides a more controlled and stable plasma concentration over time, whereas the single bolus results in a rapid peak concentration followed by a gradual decline.[24] Also, the plasma concentrations at this level may not affect the emergence time, as there was no significant difference in the emergence time of each group.

Administering a continuous infusion of a subanaesthetic dose of propofol for a duration of 3 min serves to not only decrease the peak PAED score value, but also to shorten the duration of agitation as evaluated by both the PAED and Watcha scales. Sikich and Lerman[13] who devised the PAED scale did not define a cut-off point for the presence of EA. However, Bajwa *et al*[25] suggested that a PAED score exceeding 12 demonstrates superior sensitivity and specificity compared with a threshold of 10. Consequently, we adopted a PAED score >12 as the criteria for identifying the incidence of EA. Alongside the PAED scale, we incorporated the Watcha scale due

to its simplicity and ease of application, contributing to enhanced overall precision in assessment.

The MAP was more stable during the ending of surgery, extubation and emergence in the bolus A group, the bolus B group and the continuous infusion group. The HR also increases relatively less than the control group. Subanaesthetic dose of propofol seemed to contribute to steadier MAP and HR trends during emergence, but there was no significant difference among the various administration methods.

### Limitations

Our study has several limitations. First, the study did not encompass an assessment of the safety implications associated with propofol usage, including potential airway complications and instances of apnoea. Furthermore, the selection of inguinal hernia repair as the focus of our study means that the applicability of our conclusions to different surgical contexts might be limited. Therefore, it is essential to seek further validation of our findings by exploring their implications in various other surgical procedures.

## CONCLUSIONS

Administering a continuous infusion of a subanaesthetic dose of propofol for 3 min subsequent to sevoflurane anaesthesia yielded significant reductions in the occurrence, intensity and duration of EA. Notably, this approach did not result in any extension of the emergence time.

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**Acknowledgements** The authors thank all nurses and anaesthetists for their participation in the study.

**Contributors** JC and XS contributed equally to this paper. LX is responsible for the overall content as the guarantor. All authors contributed to the study conception and design. Material preparation and data collection were performed by JC, XS, WH, LM, CL and XM. Data analysis was conducted by JC and RL. The first draft of the manuscript was written by JC and XS and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethical Committee of the Shenzhen Children's Hospital (approval number: 202205602). Written informed consent was obtained from the parents or guardians of the paediatric patients recruited to the study ( www.clinicaltrials.gov, registration number: NCT05420402).

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available on reasonable request.



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