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Effects of different doses of remifentanil combined with sevoflurane anesthesia on postoperative analgesia and hemodynamics in pediatric patients undergoing laparoscopic inguinal hernia repair

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Abstract

Background Laparoscopic inguinal hernia repair (LIHR) has the characteristics of a clear surgical field and short operation time, but it has high requirements for anesthesia. We investigated the impacts of different doses of remifentanil combined with sevoflurane anesthesia on postoperative analgesia and hemodynamics of pediatric LIHR.

Methods This randomized, double-blind and controlled study included 310 pediatric patients accepting LIHR. Excluding those failed to meet the inclusion or met the exclusion criteria, 280 patients were enrolled and randomized into the control group (sevoflurane) and the low-dose remifentanil & sevoflurane (LRS), medium-dose remifentanil & sevoflurane (MRS) and high-dose remifentanil & sevoflurane (HRS) groups (0.10, 0.20 and 0.25 μg/kg). The Behavior Pain Scale (BPS) (main observation index), Ramsay Sedation Scale (RSS), and Paediatric Anaesthesia Emergence Delirium (PAED) scores were evaluated at 1 h (T4), 3 h (T5), 6 h (T6), 8 h (T7) and 12 h (T8) postoperatively. The dynamic process of BPS, RSS and PAED scores over time was evaluated by analyzing the changes in the area under the curve (AUC) of each score during T4-T8. The changes in mean arterial pressure (MAP), heart rate (HR) and oxygen saturation (SpO_2) before the start of anesthesia (T0), 10-min after the start of surgery (T1), at the time of extubation (T2) and 30-min post-surgery (T3) and postoperative adverse reaction incidence were recorded.

Results Remifentanil & sevoflurane reduced postoperative BPS and PAED scores and increased RSS score in pediatric patients during T4-T8. The AUC_{BPS} and AUC_{PAED} in the LRS, MRS and HRS groups decreased as the remifentanil dose increased, and the AUC_{RSS} increased as the remifentanil dose rose. During T0-T3, MAP, HR and SpO_2 fluctuated greatly in the control group, but maintained good stability in the LRS, MRS and HRS groups, and the fluctuation in the HRS group was smaller. The HRS group had a lower adverse reaction incidence than the control and LRS groups.

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Conclusions Remifentanil & sevoflurane may have better effects on postoperative pain, sedation and agitation, and may be more conducive to stabilizing hemodynamics. Especially, 0.25 mg/kg remifentanil & sevoflurane have the best anesthetic effect and a low adverse reaction incidence.

Keywords Remifentanil, Sevoflurane, Laparoscopic inguinal hernia repair, Postoperative analgesia, Hemodynamics, Behavior pain scale

Background

Hernia is a common pediatric disease, with inguinal hernia as the main type and one of the most frequent surgical diseases in pediatrics [1]. Surgery is currently one of the main clinical treatments for pediatric patients with inguinal hernias, and Montupet in 1993 first proposed laparoscopic inguinal hernia repair (LIHR) in children as an alternative to traditional open hernia repair (OHR) [2, 3]. In clinical practice, LIHR is characterized by a clear surgical field and short operation time [4]. This surgery is simple in adults but complicated in children because incision discomfort agitates them, increasing the risk of bleeding and nursing difficulties [5]. Therefore, it is imperative to seek for safe and effective analgesia strategy for the treatment of inguinal hernia in pediatric practice.

Bang et al. have compared respiratory mechanics when using intravenous propofol and remifentanil vs. sevoflurane during laparoscopic colectomy and found that maintenance use of sevoflurane improves compliance and airway pressure [6]. Sevoflurane has a short onset of action and less airway irritation in children, as well as faster postoperative awakening, but it has a high incidence of postoperative emergence of sexual agitation caused by postoperative pain [7–9]. Of note, remifentanil, as a novel narcotic analgesic belonging to the fentanyl family, and an agonist of fentanyl μ-type opioid receptor, exerts a potent analgesic effect, primarily through non-specific esterase metabolism [10]. Remifentanil possesses advantageous attributes for neonatal anesthesia, including swift onset, strong analgesic efficacy, and rapid clearance [11]. Remifentanil has been proposed to reduce the incidence of emerging agitation following sevoflurane anesthesia in children [12]. Indeed, avoiding opioid boluses reduces hemodynamic and anesthesia/analgesia depth variations, and remifentanil is the only therapeutically accessible opioid that does not accumulate with extended intravenous infusion, while morphine, fentanyl, and sufentanil do [13]. Additionally, remifentanil demonstrates a faster emergence from anesthesia relative to fentanyl, as observed in endoscopic procedures [14]. This study aimed to investigate the effects of different doses of remifentanil combined with sevoflurane anesthesia on postoperative analgesia and hemodynamics in pediatric laparoscopy, providing relevant theoretical references for the clinical anesthetic management of pediatric LIHR.

Methods

Ethics statement

The study was reviewed and approved by the medical ethics committee of Shandong Provincial Hospital Affiliated to Shandong First Medical University and conformed to the Declaration of Helsinki (registration number: 2019 – 0141, registration date: 15/12/2019). All subject children and their guardians provided informed consent forms.

Sample size calculation and statistical power analysis

The sample size for this study was calculated using Gpower software (V3.0.10, University of Düsseldorf, Germany) [15]. The independent sample *t* test was used for comparisons between two groups, and the initial parameter was set as Effect Size = 0.5, $\alpha = 0.05$, and Power $(1\text{-}\beta) = 0.80$. All pediatric patients were randomized into 4 groups in the ratio of 1:1:1:1, with a minimum sample size of 64 in each group. Considering the loss rate of 10%, at least 70 cases were eventually needed in each group. Statistical efficacy analysis was performed afterward, and the main observation index Behavior Pain Scale (BPS) score was selected as the calculation index. The Effect size d value for BPS score at T6 (when the difference in PBS score readings was the largest) between the control and LRS groups was calculated to be 0.82 under the formula: Effect size d = mean difference between the two groups/standard deviation after combining the two groups. Then, the statistical power $(1\text{-}\beta)$ calculated using Gpower software was 0.998. This showed that the sample size of this study had a high enough confidence level to illustrate the reliability of the results of this study.

Study subjects

In this randomized, double-blind (participants: no access to group assignment documents; investigators: standardized protocols masked drug differences; outcome assessors: trained to avoid bias with validated tools), and controlled study, a total of 310 pediatric patients who underwent laparoscopic inguinal hernia repair (LIHR) in Shandong Provincial Hospital Affiliated to Shandong First Medical University from January 2020 to April 2023 were included. Among them, 298 met the inclusion criteria, and 18 were excluded based on the exclusion criteria. No patients withdrew from the study. Excluding those who failed to meet the inclusion or exclusion criteria, 280 patients were enrolled and randomized into 4 groups

using the computerized random grouping method, with 70 cases in each group (Supplementary Fig. 1). This was a randomized, double-blind, controlled study, in which a full-time researcher was responsible for placing a computer-generated random number table in a sealed opaque envelope before surgery and placing it in the medical record in the operational morning, without the awareness of the grouping by the patients or subsequent anesthesiologists or surgical staffs. Additionally, an anesthesia nurse who was not involved in this study was responsible for configuring the analgesic pump. Baseline information such as age, sex, body mass index (BMI) and operation time were recorded for pediatric patients.

Inclusion criteria were as below: [1] diagnosed as requiring LIHR; [2] aged 2 to 8 years; [3] with no coagulation dysfunction; [4] American Society of Anesthesiologists (ASA) classification I-II.

Exclusion criteria were as follows: [1] combined with cardiac, renal and other organic dysfunctions; [2] with mental abnormalities and communication difficulties; [3] with respiratory tract infection and pulmonary inflammation; [4] with allergic constitution or contraindications; [5] with strangulated or incarcerated hernia; [6] with inguinal area tumor or trauma.

Grouping

All children were randomized to the following groups ($n=70$): [1] the control group: after induction of conventional anesthesia, children were given 2–3% sevoflurane to maintain anesthesia; [2] the study group included the low/medium/high dose remifentanil + sevoflurane groups (LRS/MRS/HRS): after routine anesthesia induction, children were given low/medium/high doses (0.10/0.20/0.25 μg/kg) of remifentanil + 2-3% sevoflurane for anesthesia maintenance. The specific steps and medication use were described in the anesthesia regimen. There were no significant differences in terms of age, sex, BMI, operation time and ASA classification among the four groups (all $P>0.05$, Table 1).

Anesthesia regimen

Anesthesia induction

All pediatric patients underwent a 6-h fast and a 2-h drinking fast preoperatively. Intramuscular injection of 0.02 mg/kg atropine (Changjiang Pharmaceutical, Wuhu, Anhui, China) was given 30 min before surgery. After admission to the operating room, the patient information was first checked, and intravenous access was routinely established. The vital signs of pediatric patients such as mean arterial pressure (MAP), heart rate (HR) and saturation of peripheral oxygen (SpO_2) were monitored. All patients were given an intravenous injection with 0.2 mg/kg dexamethasone sodium phosphate injection (Jinyao Pharmaceutical, Tianjin, China) and 0.1 mg/kg midazolam injection (Nhwa Pharmaceutical, Xuzhou, Jiangsu, China). After the patients were observed to be emotionally stable, they were given 2 mg/kg propofol emulsion injection (Aspen Pharma Trading Limited, Ireland, UK) and oxygen inhalation. Next, patients were given an intravenous injection with 0.5 mg/kg atracurium besilate (Hengrui Pharmaceutical, Shanghai, China) and 2.0×10^{-3} mg/kg fentanyl citrate injection (Humanwell Pharmaceutical, Yichang, Hubei, China). Upon non-invasive assisted breathing, they were subjected to endotracheal intubation or laryngeal mask placement, and the ventilator was connected. For children aged 8 years and older, laryngeal masks were used, while for those under 8 years old, endotracheal intubation was adopted, with no significant differences between groups. In this study, different airway management methods were selected based on the children's age and surgical requirements. Endotracheal intubation is the preferred airway management technique for children under 8 years old, as it ensures airway safety. Therefore, we used endotracheal intubation for children under 8 years old. For children aged 8 years and older, who had more mature airway development, laryngeal mask placement has a higher success rate, which provides adequate airway protection, and reduces complications associated with endotracheal intubation, such as vocal cord injury and postoperative sore throat. Therefore, we used laryngeal masks in this age group. The use of laryngeal masks adhered to the criteria

Table 1 Comparisons of clinical baseline data of the pediatric patients among the four groups

Group	Age (years)	Sex (cases)		Body mass index (kg)	Operation time (min)	ASA classification (I/II)
		Male	Female			
Control ($n=70$)	4 (2,7)	38	32	8.92 ± 1.61	16.54 ± 4.68	48/22
LRS ($n=70$)	5 (2,8)	40	30	9.02 ± 1.84	17.06 ± 5.04	44/26
MRS ($n=70$)	6 (2,8)	36	34	9.68 ± 1.81	16.92 ± 5.21	45/25
HRS ($n=70$)	5 (3,6)	37	33	9.24 ± 1.95	17.35 ± 5.18	46/24
P value	0.0820	0.9182		0.0644	0.8158	0.9073

Note: The Shapiro-Wilk test was used to test for normal distribution, and the measurement data of normal distribution were expressed as mean ± standard deviation, which were analyzed using one-way ANOVA), followed by Tukey's test. Non-normally distributed measurement data were expressed in quartiles [median (minimal, maximal)] and analyzed using the Kruskal-Wallis H test. Categorical variables were expressed using the number of cases and analyzed by the Chi-square test. Values of $P<0.05$ were considered to be statistically significant

of "Only ASA I patients with BMI < 85th percentile" and was simultaneously monitored for "continuous capnography and airway pressure (< 20 cmH_2O)" [16, 17].

Anesthesia maintenance

The control group: Anesthesia was maintained with 2–3% sevoflurane (Hengrui Pharmaceutical) through nebulized inhalation. After anesthesia induction, patients underwent intermittent intravenous infusion of 0.02 mg/kg vecuronium bromide (Biolab, Beijing, China) at 30-min intervals to maintain muscle relaxation. Anesthesia machine parameters were maintained as follows: pressure at 8–15 mmHg, tidal volume at 10 mL/kg, and respiratory rate at 18–25 breaths per min. The fresh gas flow rate was set at 1–2 L/min.

The study group: On the basis of the control group, patients in the study groups underwent continuous infusion of varying doses of remifentanil hydrochloride (0.10, 0.20, and 0.25 μg/kg) (Humanwell Pharmaceutical), with the sevoflurane dosage adjusted during the operation. Specifically, the study group was given a standard dose of sevoflurane (2–3%) to establish the depth of anesthesia. After administering remifentanil infusion, the patients were administered sevoflurane with the concentration reduced by 0.3% every 5 min until the bispectral index reached 50–60 and the MAP fluctuation remained within 15% of the base value during surgical stimulation to prevent deep anesthesia.

Intraoperative monitoring and postoperative care

The pediatric patients kept breathing smoothly during the operation. If the systolic blood pressure was below 90 mmHg or 70% of the preoperative pressure, an intravenous injection of 0.1 mg/kg ephedrine or an intravenous infusion of 0.1 μg/kg/min phenylephrine was administered. When SpO_2 was lower than 90%, the causes of hypoxemia, such as airway obstruction and insufficient ventilation, were first evaluated and corrected, and hypoxemia was quickly corrected by adjusting airway management, optimizing ventilation parameters, and using drugs. If the child had cardiac arrest, cardiac compression would be taken. If HR was lower than 60 beats/min, 0.02 mg/kg intravenous atropine should be administered. Meanwhile, vital signs during anesthesia and surgery should be closely monitored, and timely targeted treatment should be given. The intravenous injection of vecuronium bromide was stopped 30 min before the completion of the surgery. Sevoflurane use was discontinued 5 min before the completion of surgery. After operation, the child was ensured to recover spontaneous breathing, open eyes, and swallowing reflex, with 10-min breathing and SpO_2 > 95%. The endotracheal tube or laryngeal mask was removed after aspiration of oral and tracheal secretions.

Observation and evaluation indicators

The main observation index of this study was the BPS score, which was used to evaluate the analgesic effect. The secondary observation indexes were the Ramsay Sedation Scale (RSS) score, Pediatric Anesthesia Emergence Delirium (PAED) score, hemodynamic indexes and adverse reactions.

The BPS score, RSS score and PAED score, as well as the area under the curve (AUC) for each score (AUC, AUC_{BPS}, AUC_{RSS}, AUC_{PAED}) were recorded at 1 h (T4), 3 h (T5), 6 h (T6), 8 h (T7) and 12 h (T8) after surgery. The area under the curve (AUC) refers to the total area under the curve of score changing with time. It was obtained by multiplying the score of each time point with the corresponding period and then accumulating the areas of all periods. AUC was a holistic and cumulative quantitative indicator.

The pain was scored using BPS (1, no physical movement; 2, slightly painful expression; 3, desire to move the body; 4, painful expression with obvious moaning and agitation; 5, unbearable pain) [18].

Sedation was scored using RSS (1, anxious and restless; 2, cooperative, oriented, and quiet; 3, responsive to commands; 4, drowsy and quickly responsive to light browbeating or loud auditory stimuli; 5, drowsy and slowly responsive to light browbeating or loud auditory stimuli; 6, drowsy and unresponsive) [19].

Agitation was evaluated using the PAED score, including the children's degree of inability to be calmed, whether the behavior was purposeful, degree of agitation, awareness of surroundings, and ability to make eye contact with parents or health care providers [20]. Each item had 5 levels (corresponding to 0–4 points), and all the scores were added up after level determination, with the higher score representing a more likely agitation situation. A score of > 16 was determined to be agitation during the awakening period of general anesthesia.

Hemodynamic indexes, including the changes in MAP, HR and SpO_2 before anesthesia (T0), 10 min after the start of surgery (T1), at the time of extubation (T2) and 30 min after surgery (T3) were documented. Adverse reactions such as nausea, vomiting and agitation were also recorded.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 8.0 software (GraphPad Software, San Diego, CA, USA). The Shapiro-Wilk test was used to test for normal distribution, and the measurement data of the normal distribution were expressed as mean ± standard deviation (SD). The one-way analysis of variance (ANOVA) was used to compare the difference of single index among multiple groups, and the two-way ANOVA was used to compare the differences at different time points among multiple

Table 2 Effect of different doses of remifentanil combined with Sevoflurane anesthesia on BPS score post pediatric LIHR

Group	Time	BPS score	[a]*P* value	[b]*P* value
control (*n* = 70)	T4	2.55 ± 0.41	-	-
	T5	3.20 ± 0.42	< 0.0001	-
	T6	3.87 ± 0.39	< 0.0001	-
	T7	3.45 ± 0.45	< 0.0001	-
	T8	2.98 ± 0.46	< 0.0001	-
LRS (*n* = 70)	T4	2.38 ± 0.38	-	0.0350
	T5	2.86 ± 0.37	< 0.0001	0.0008
	T6	3.50 ± 0.41	< 0.0001	< 0.0001
	T7	3.07 ± 0.36	< 0.0001	< 0.0001
	T8	2.40 ± 0.44	0.9978	< 0.0001
MRS (*n* = 70)	T4	2.13 ± 0.31	-	< 0.0001
	T5	2.66 ± 0.35	< 0.0001	< 0.0001
	T6	3.21 ± 0.41	< 0.0001	< 0.0001
	T7	2.59 ± 0.39	< 0.0001	< 0.0001
	T8	2.16 ± 0.34	0.9894	< 0.0001
HRS (*n* = 70)	T4	1.88 ± 0.30	-	< 0.0001
	T5	2.30 ± 0.28	< 0.0001	< 0.0001
	T6	2.84 ± 0.33	< 0.0001	< 0.0001
	T7	2.26 ± 0.30	< 0.0001	< 0.0001
	T8	1.94 ± 0.25	0.8754	< 0.0001

Note: The two-way ANOVA was used to compare the differences between different time points (T4-T8) in the same group and between different groups, followed by Tukey's multiple comparison test; 1-h post operation (T4), 3-h post operation (T5), 6-h post operation (T6), 8-h post operation (T7), 12-h post operation (T8); [a]*P* represented comparisons of different time points (T5, T6, T7, T8) with T4 time point in the same group; [b]*P* indicated comparisons to the control group at the same time points (T4, T5, T6, T7, T8)

Table 3 Effect of different doses of remifentanil combined with Sevoflurane anesthesia on the RSS score in pediatric patients post LIHR

Group	Time	RSS score	[a]*P* value	[b]*P* value
control (*n* = 70)	T4	4.46 ± 0.36	-	-
	T5	3.78 ± 0.33	< 0.0001	-
	T6	3.42 ± 0.34	< 0.0001	-
	T7	2.63 ± 0.41	< 0.0001	-
	T8	2.10 ± 0.37	< 0.0001	-
LRS (*n* = 70)	T4	4.53 ± 0.37	-	0.6050
	T5	3.86 ± 0.35	< 0.0001	0.4927
	T6	3.53 ± 0.32	< 0.0001	0.2119
	T7	2.87 ± 0.36	< 0.0001	0.0001
	T8	2.64 ± 0.33	< 0.0001	< 0.0001
MRS (*n* = 70)	T4	4.69 ± 0.32	-	0.0003
	T5	3.98 ± 0.31	< 0.0001	0.2119
	T6	3.62 ± 0.30	< 0.0001	0.0024
	T7	2.96 ± 0.29	< 0.0001	< 0.0001
	T8	2.81 ± 0.33	< 0.0001	< 0.0001
HRS (*n* = 70)	T4	4.88 ± 0.34	-	< 0.0001
	T5	4.46 ± 0.35	< 0.0001	< 0.0001
	T6	4.02 ± 0.33	< 0.0001	< 0.0001
	T7	3.44 ± 0.30	< 0.0001	< 0.0001
	T8	3.01 ± 0.27	< 0.0001	< 0.0001

Note: The two-way ANOVA was used to compare the differences between different time points (T4-T8) in the same group and between different groups, followed by Tukey's multiple comparison test; 1-h post operation (T4), 3-h post operation (T5), 6-h post operation (T6), 8-h post operation (T7), 12-h post operation (T8); [a]*P* represented comparisons of different time points (T5, T6, T7, T8) with T4 time point in the same group; [b]*P* indicated comparisons to the control group at the same time points (T4, T5, T6, T7, T8)

groups and analyze the interaction between group and time, followed by Tukey's multiple comparisons test. The measurement data of non-normal distribution were expressed by quartiles [median value (minimum value, maximum value)] and examined using the Kruskal-Wallis H test. Categorical variables were expressed using the number of cases and analyzed by the Chi-square test. Values of $P < 0.05$ were considered to be statistically significant.

Results

Effect of different doses of remifentanil combined with Sevoflurane anesthesia on analgesia post pediatric laparoscopy

We evaluated postoperative analgesia and sedation at T4-T8 using BPS (main observation index) and RSS scores, respectively. The results of the two-way ANOVA indicated that all main effects (group and time point) as well as their interaction were highly significant (all $P < 0.0001$), i.e., group, time point, and their interaction had significant impacts on BPS and RSS scores (Supplementary Tables 1–2).

As illustrated in Tables 2 and 3, the results of the Tukey's multiple comparison test revealed that the BPS scores at T4-T8 in the control group exhibited a pattern of initial growth, followed by a decline and a subsequent increase, the RSS scores showed a continuous downward trend, and the discrepancies were statistically significant (all $P < 0.05$). More than that, the BPS scores in the LRS, MRS and HRS groups were significantly lower than that in the control group; the decrease in the MRS and HRS groups was greater, which might be dose-dependent. There was no significant difference in the RSS score between the LRS group and the control group at T4-T6, and the RSS score was higher at T7-T8 in the LRS group than in the control group; in the MRS group, the RSS score was not significantly different from that of the control group at T5, and had higher values at the T4 and T6-T8 compared with the control group; the RSS scores at T4-T8 in the HRS group were higher than that in the control group (all $P > 0.05$).

Additionally, we analyzed the AUCs of RSS and BPS scores during T4-T8 by GraphPad Prism 8.01, in a bid to explore the effect of drugs on pain relief and sedation after they entered the body circulation. Based on the results (Fig. 1A-B), compared with the control group, with the rising of remifentanil dose, AUC_{BPS} decreased and AUC_{RSS} increased in the LRS, MRS and HRS groups,

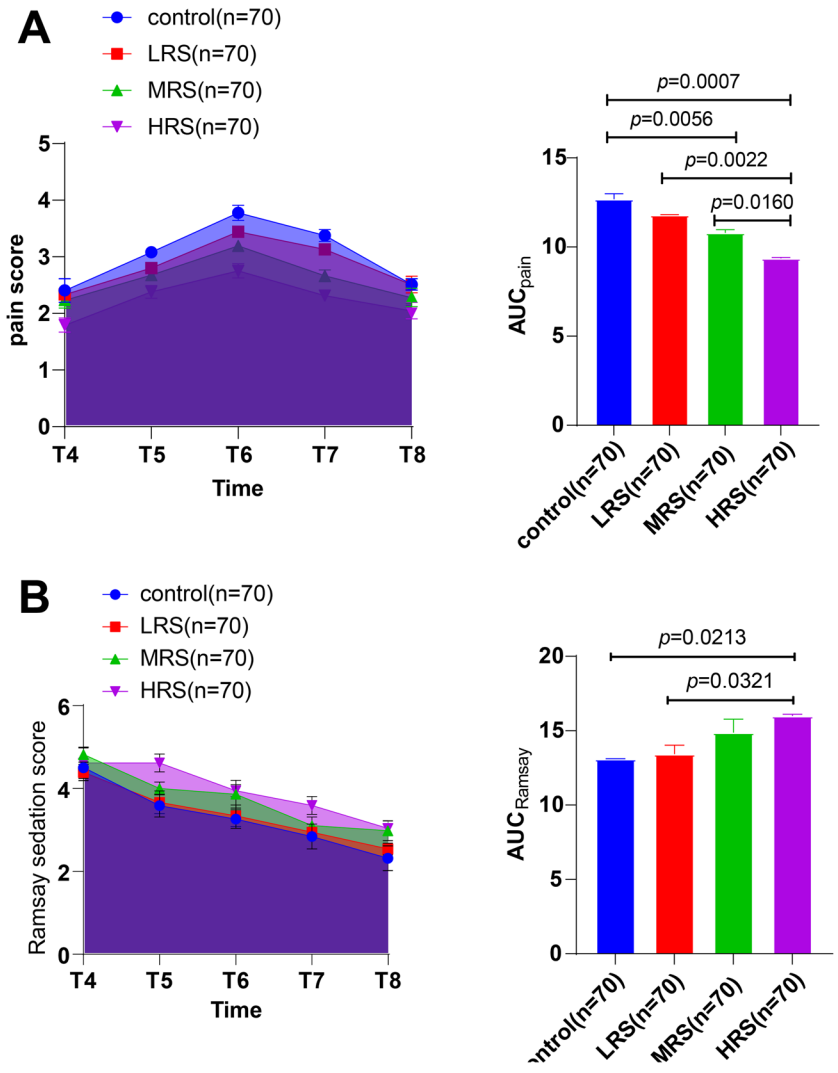

Fig. 1 Impact of varying dosages of remifentanil in conjunction with sevoflurane anesthesia on postoperative analgesia following pediatric laparoscopy. GraphPad Prism 8.01 software was used to analyze the AUCs of BPS score (**A**) and RSS score (**B**) during T4-T8. AUC refers to the total area under the curve of score changing with time. It was obtained by multiplying the score of each time point with the corresponding period and then accumulating the areas of all periods. A decrease in AUC_{BPS} indicated a better analgesic effect during the postoperative anesthesia awakening period; an increase in AUC_{RSS} indicated better sedation during the postoperative anesthesia awakening period; one-way ANOVA was used for comparisons among multiple groups; 1-h post operation (T4), 3-h post operation (T5), 6-h post operation (T6), 8-h post operation (T7), 12-h post operation (T8)

but no significant difference in AUC_{BPS} was found between the MRS and HRS groups.

Effect of different doses of remifentanil combined with sevoflurane anesthesia on PAED scores after pediatric LIHR.

We utilized the PAED score to assess the postoperative agitation. The results of the two-way ANOVA showed that both group and time point had significant effects on the PAED score (Supplementary Table 3, all $P<0.0001$), while their interaction had no significant effect on the PAED score ($P=0.6521$).

The results of the Tukey's multiple comparison test (Table 4) showed that the PAED scores in the control, LRS and MRS groups at T5-T8 compared to T4 showed trends of increasing first, then decreasing and then increasing (all $P<0.05$), while the score didn't obviously vary in the HRS group ($P>0.05$). Compared with the control group, the PAED scores in the LRS, MRS and HRS groups were significantly decreased at T4-T8, and the score in the HRS group was lower than in the LRS and MRS groups ($P<0.05$). Additionally, the AUC_{PAED} of children in the LRS, MRS and HRS groups declined with the increase of remifentanil dose in contrast with the control group (Fig. 2).

Table 4 Effect of different doses of remifentanil combined with Sevoflurane anesthesia on PAED score after pediatric LIHR

Group	Time	PAED score	[a]*P* value	[b]*P* value
control (*n* = 70)	T4	12.64 ± 3.00	-	-
	T5	13.91 ± 2.55	0.1120	-
	T6	14.56 ± 2.20	0.0025	-
	T7	13.09 ± 3.16	0.1224	-
	T8	12.84 ± 3.18	0.9956	-
LRS (*n* = 70)	T4	11.06 ± 4.02	-	0.0144
	T5	11.56 ± 4.00	0.8769	< 0.0001
	T6	12.82 ± 3.98	0.0075	0.0053
	T7	12.30 ± 3.96	0.1278	0.0136
	T8	11.30 ± 4.05	0.9911	0.0182
MRS (*n* = 70)	T4	9.52 ± 3.11	-	< 0.0001
	T5	10.12 ± 3.10	0.7848	< 0.0001
	T6	11.50 ± 3.06	0.0016	< 0.0001
	T7	10.31 ± 3.13	0.5614	< 0.0001
	T8	9.80 ± 3.05	0.9840	< 0.0001
HRS (*n* = 70)	T4	7.66 ± 2.24	-	< 0.0001
	T5	8.36 ± 2.25	0.6720	< 0.0001
	T6	8.69 ± 2.29	0.2873	< 0.0001
	T7	8.53 ± 2.27	0.3815	< 0.0001
	T8	8.60 ± 2.26	0.9707	< 0.0001

Note: The two-way ANOVA was used to compare the differences between different time points (T4-T8) in the same group and between different groups, followed by the Tukey's multiple comparison test; 1-h post operation (T4), 3-h post operation (T5), 6-h post operation (T6), 8-h post operation (T7), 12-h post operation (T8); [a]*P* represented comparisons of different time points (T5, T6, T7, T8) with T4 time point in the same group; [b]*P* indicated comparisons to the control group at the same time points (T4, T5, T6, T7, T8)

Effect of different doses of remifentanil combined with Sevoflurane anesthesia on hemodynamics in pediatric LIHR

The changes in hemodynamic indexes (MAP, HR and SpO_2) were recorded at T0-T3. The two-way ANOVA results indicated that group, time point, and their interaction had significant effects on MAP and HR (Supplementary Tables 4–5, all $P < 0.0001$). However, neither group nor the interaction had a significant effect on SpO_2 (Supplementary Table 6, all $P > 0.05$), whereas time point had a significant effect on SpO_2 ($P = 0.0386$).

The results (Tables 5, 6 and 7) of Tukey's multiple comparison test illustrated that there was no significant difference in baseline MAP, HR or SpO_2 level among the control, LRS, MRS and HRS groups at T0 ($P > 0.05$). In the control group, compared with T0, MAP increased first, then decreased and then elevated at T1-T3 ($P < 0.05$); HR increased first and then declined, and showed no significant difference between T3 and T0; SpO_2 did not change significantly. Compared with the control group, the readings of MAP, HR and SpO_2 in the LRS, MRS and HRS groups remained relatively stable at T1-T3 relative to T0. Therefore, the intraoperative hemodynamic indexes in the control group fluctuated greatly, while those in the LRS, MRS and HRS groups fluctuated relatively less, and the fluctuation in the HRS group was smaller than that in the LRS and MRS groups.

Comparative analysis of adverse reactions

Finally, the statistical analysis of the incidence of adverse reactions such as nausea, vomiting and agitation revealed that the difference in the incidence of adverse reactions among pediatric patients in the control, LRS and MRS

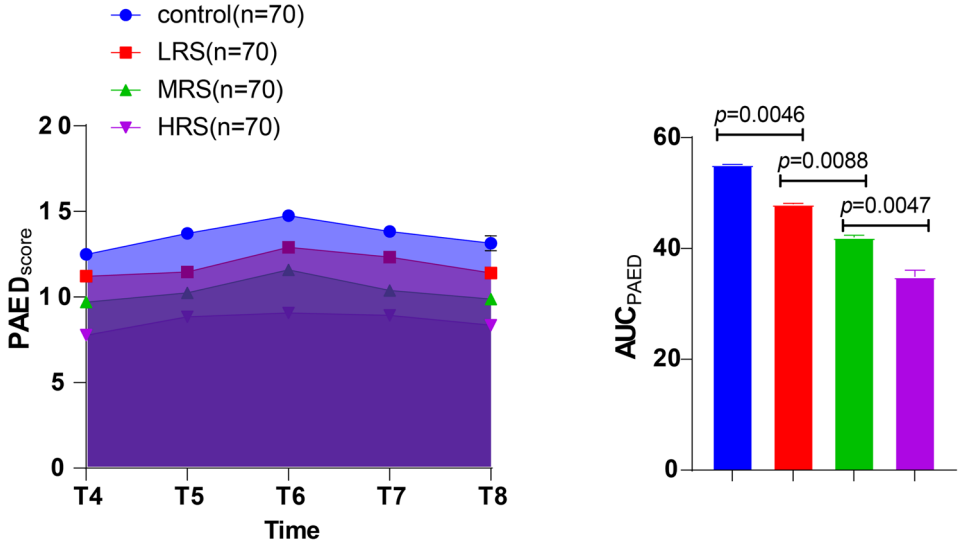

Fig. 2 Impact of various dosages of remifentanil together with sevoflurane anesthesia on PAED score of pediatric patients post LIHR. GraphPad Prism 8.01 software was used to analyze the AUC (B) of the PAED score at T4-T8. AUC refers to the total area under the curve of score changing with time. It was obtained by multiplying the score of each time point with the corresponding period, and then accumulating the areas of all periods. A decrease in AUC_{PAED} indicated a decrease in the incidence of delirium during the postoperative anesthesia awakening period. One-way ANOVA was used for comparisons among multiple groups; 1-h post operation (T4), 3-h post operation (T5), 6-h post operation (T6), 8-h post operation (T7), 12-h post operation (T8)

Table 5 Effect of different doses of remifentanil combined with Sevoflurane anesthesia on MAP in pediatric LIHR

Group	Time	MAP (mmHg)	[a]*P* value	[b]*P* value
control (*n* = 70)	T0	106.85 ± 14.26	-	-
	T1	129.31 ± 15.62	< 0.0001	-
	T2	108.62 ± 11.25	0.8111	-
	T3	115.62 ± 12.37	< 0.0001	-
LRS (*n* = 70)	T0	102.32 ± 13.01	-	0.1050
	T1	106.85 ± 12.84	0.1050	< 0.0001
	T2	96.85 ± 9.12	0.0313	< 0.0001
	T3	101.52 ± 8.94	0.9781	< 0.0001
MRS (*n* = 70)	T0	103.14 ± 12.01	-	0.2455
	T1	105.85 ± 13.34	0.5251	< 0.0001
	T2	98.81 ± 9.02	0.1316	< 0.0001
	T3	101.69 ± 10.36	0.8861	< 0.0001
HRS (*n* = 70)	T0	102.32 ± 11.38	-	0.1050
	T1	104.62 ± 13.14	0.6561	< 0.0001
	T2	99.15 ± 9.29	0.3845	0.0001
	T3	102.04 ± 10.06	0.9990	< 0.0001

Note: The two-way ANOVA was used to compare the differences between different time points (T0-T3) in the same group and between different groups, followed by the Tukey's multiple comparison test; before anesthesia (T0), 10-min after the start of operation (T1), at the time of extubation (T2) and 30-min after operation (T3); [a]*P* represented comparisons of different time points (T1, T2, T3) with T0 time point in the same group; [b]*P* indicated comparisons to the control group at the same time points (T0, T1, T2, T3)

Table 6 Effect of different doses of remifentanil combined with Sevoflurane anesthesia on HR in pediatric LIHR

Group	Time	HR (beat/min)	[a]*P* value	[b]*P* value
control (*n* = 70)	T0	105.54 ± 8.35	-	-
	T1	115.72 ± 9.26	< 0.0001	-
	T2	123.34 ± 10.52	< 0.0001	-
	T3	108.54 ± 8.55	0.2002	-
LRS (*n* = 70)	T0	104.92 ± 8.32	-	0.9772
	T1	109.16 ± 8.55	0.0280	0.0001
	T2	112.22 ± 9.59	< 0.0001	< 0.0001
	T3	106.96 ± 8.38	0.5380	0.7276
MRS (*n* = 70)	T0	105.22 ± 8.86	-	0.9967
	T1	108.32 ± 9.53	0.1757	< 0.0001
	T2	109.52 ± 9.21	0.0250	< 0.0001
	T3	106.71 ± 8.89	0.7619	0.6261
HRS (*n* = 70)	T0	105.82 ± 8.57	-	0.9978
	T1	108.54 ± 9.93	0.2807	< 0.0001
	T2	107.34 ± 8.95	0.7506	< 0.0001
	T3	105.12 ± 8.38	0.9678	0.1119

Note: The two-way ANOVA was used to compare the differences between different time points (T0-T3) in the same group and between different groups, followed by the Tukey's multiple comparison test; before anesthesia (T0), 10-min after the start of operation (T1), at the time of extubation (T2) and 30-min after operation (T3); [a]*P* represented comparisons of different time points (T1, T2, T3) with T0 time point in the same group; [b]*P* indicated comparisons to the control group at the same time points (T0, T1, T2, T3)

groups was not statistically significant ($P > 0.05$), while the incidence in the HRS group was markedly lowered relative to the control and LRS groups (all $P < 0.05$, Table 8).

Table 7 Effects of different doses of remifentanil combined with Sevoflurane anesthesia on SpO_2 in pediatric LIHR

Group	Time	SpO_2 (%)	[a]*P* value	[b]*P* value
control (*n* = 70)	T0	98.45 ± 0.75	-	-
	T1	98.51 ± 0.68	0.9622	-
	T2	98.37 ± 0.72	0.9163	-
	T3	98.25 ± 0.67	0.3679	-
LRS (*n* = 70)	T0	98.37 ± 0.73	-	0.9144
	T1	98.41 ± 0.61	0.9883	0.8466
	T2	98.32 ± 0.84	0.9776	0.9770
	T3	98.24 ± 0.67	0.7183	0.9998
MRS (*n* = 70)	T0	98.35 ± 0.71	-	0.8466
	T1	98.28 ± 0.75	0.9405	0.2379
	T2	98.26 ± 0.74	0.8830	0.8057
	T3	98.18 ± 0.73	0.5068	0.9405
HRS (*n* = 70)	T0	98.31 ± 0.79	-	0.6626
	T1	98.51 ± 0.69	0.3602	0.9999
	T2	98.25 ± 0.72	0.9613	0.7609
	T3	98.39 ± 0.76	0.9144	0.6626

Note: The two-way ANOVA was used to compare the differences between different time points (T0-T3) in the same group and between different groups, followed by the Tukey's multiple comparison test; before anesthesia (T0), 10-min after the start of operation (T1), at the time of extubation (T2) and 30-min after operation (T3); [a]*P* represented comparisons of different time points (T1, T2, T3) with T0 time point in the same group; [b]*P* indicated comparisons to the control group at the same time points (T0, T1, T2, T3)

Discussion

OHR has long been the preferred method for most surgeons and is generally recommended as the best therapy for inguinal hernia [21]. It is also noteworthy that LIHR has recently gained popularity, and some surgeons appreciate it for significantly reducing the incidence of long-term postoperative pain [22]. However, LIHR is an invasive treatment that can cause an intense stress response and hemodynamic alterations, which may eventually compromise the immune system and raise the likelihood of postoperative infections [23]. Therefore, the selection of an anesthesia method is crucial for achieving successful surgical outcomes, making it imperative to identify a scientific and safe anesthetic technique [24]. As reported, the sevoflurane inhalation anesthesia is becoming increasingly extensive, while sevoflurane has been demonstrated to generate stress responses of different degrees during LIHR [25]. Encouragingly, remifentanil, a μ-opioid receptor agonist that exhibits analgesic potency comparable to fentanyl, is suitable for opioid-based anesthesia in pediatric patients given its ability to maintain hemodynamic stability, promote recovery quickly, and minimize postoperative side effects [26, 27]. In this paper, we aimed to unveil the impacts of different doses of remifentanil combined with sevoflurane anesthesia on postoperative analgesia and hemodynamics of pediatric LIHR.

The primary aim of general anesthesia is to minimize hemodynamic fluctuations to avoid a swift rise in blood

Table 8 Comparative analysis of adverse reactions

Group	Nausea	Vomiting	Agitation	Total incidence	[a]*P* value	[b]*P* value
control ($n=70$)	3 (4.29%)	4 (5.71%)	9 (12.86%)	16 (22.86%)	-	-
LRS ($n=70$)	2 (2.86%)	5 (4.29%)	8 (10.00%)	15 (21.43%)	0.8387	-
MRS ($n=70$)	3 (4.29%)	3 (4.29%)	6 (8.57%)	12 (17.14%)	0.3980	0.5205
HRS ($n=70$)	2 (2.86%)	1 (1.43%)	3 (4.29%)	5 (8.57%)*#	0.0202	0.0332

Note: Categorical variables were expressed using the number of cases, followed by the Chi-square test; [a]*P* indicated comparisons with the control group; [b]*P* indicated comparisons with the LRS group

pressure and HR during intubation and capnoperitoneum and the evident reduction before capnoperitoneum [23]. In this study, we discovered that compared with the control group, the readings of MAP, HR and SpO_2 in pediatric patients treated with sevoflurane & remifentanil remained relatively stable at T1-T3 compared with T0, suggesting that remifentanil combined with sevoflurane might be more conducive to the stability of hemodynamics. Moreover, a thorough pain assessment is necessary for optimum pain treatment and critical illness-related agitation and delirium treatment [28]. The BPS scale is utilized more frequently than other pain behavioral monitoring scales, and it is valid and sensitive in detecting changes in pain response among patients receiving sedatives or those with communication impairments [29]. We mainly found that BPS scores of the LRS, MRS, and HRS groups were significantly lower than those of the Control group, with the reductions in the MRS and HRS groups being more pronounced, indicating a potential dose-dependent relationship. According to the evaluations of RSS, PAED, and BPS scores, as the dosage of remifentanil was raised, there was an initial rise followed by a decline in BPS and PAED scores, with their AUCs exhibiting downward trends; nevertheless, the RSS score continually dropped, and the AUC_{RSS} demonstrated an upward trend, underscoring that the more the drug enters the systemic circulation, the more evident the effects on mitigating pain, sedation and agitation. All these findings uncovered that anesthesia with sevoflurane and remifentanil combination was effective in postoperative analgesia and hemodynamics of pediatric LIHR.

Moreover, the most important finding of our paper was that the combination of remifentanil (especially 0.25 μg/kg) and sevoflurane is more beneficial in stabilizing the hemodynamics, reducing postoperative pain and agitation, and decreasing the incidence of adverse effects. In a similar line of evidence, the concurrent administration of propofol and remifentanil is extensively employed in the field of anesthesia to induce drowsiness and provide analgesia during short-term medical procedures in healthy volunteers with a mean age of 26.5 [30]. Remifentanil alone is not capable of producing enough sedation, but it can enhance the sedative impact of propofol or sevoflurane when provided together, due to the synergistic action of the opioids and sedatives in patients undergoing elective cardiac valve repair or replacement surgery [31]. Furthermore, Zhang et al. have reported that remifentanil coupled with ketorolac tromethamine may effectively ameliorate pain and restlessness during recovery from general anesthesia while minimizing the risk of adverse effects in patients who underwent partial or total thyroidectomy (20–65 years old) [32]. All these articles have confirmed that remifentanil combined with other anesthetic drugs can have a better anesthetic effect. Based on the hypothesis and findings, it was plausible that the combined application of remifentanil and sevoflurane had a better therapeutic effect on postoperative analgesia for pediatric patients receiving LIHR.

In conclusion, this study prospectively investigated the effects of different doses of remifentanil (0.10 μg/kg, 0.20 μg/kg, and 0.25 μg/kg) combined with sevoflurane on postoperative analgesia and hemodynamics of LIHR and revealed that remifentanil combined with sevoflurane was more beneficial to stabilize hemodynamics, reduce postoperative pain, and decrease agitation in pediatric patients. In particular, 0.25 μg/kg remifentanil combined with sevoflurane demonstrated significant benefits in postoperative analgesia and hemodynamics.

Nevertheless, our study has several limitations. Firstly, the sample size included is small, and surgery-related indicators such as pre- and post-operative inflammatory factors and postoperative recovery time are not analyzed. Secondly, the study was limited to a specific pediatric population (2–8 years old) who underwent LIHR. Future research will investigate the effects of remifentanil in other surgical procedures and across a broader age range. Thirdly, our study did not account for the possibility that an escalation in opioid dosage might elevate the incidence of vomiting in pediatric patients. Fourthly, the selection of appropriate statistical methods and models is crucial for obtaining effective analysis results. For instance, using multilevel hierarchical models is a more flexible approach compared to two-way ANOVA. Therefore, expanding the sample size and selecting better statistical analysis will further improve our research.

Supplementary Information

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Supplementary Material 1: CONSORT flow chart.

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

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Author contributions
Conceptualization, JM and SH; Methodology, JM and SH; Software, YW; Validation, JM, YW and ZL; Formal Analysis, SH; Investigation, ZL; Resources, YW; Data Curation, JM; Writing– Original Draft Preparation, JM; Writing– Review & Editing, SH; Visualization, YW; Supervision, ZL; Project Administration, SH.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Human ethics and consent to participate
The study was reviewed and approved by the medical ethics committee of Shandong Provincial Hospital Affiliated to Shandong First Medical University and conformed to the Declaration of Helsinki (registration number: 2019 – 0141, registration date: 15/12/2019). All subject children and their guardians provided informed consent forms.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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