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ORIGINAL RESEARCH

# Comparative analysis of the efficacy and safety of hydromorphone and sufentanil as postoperative analgesia in children: a double-blind, prospective, randomized, and multicentered controlled trial

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## Abstract

The efficacy and safety data of sufentanil or hydromorphone usage are limited for children undergone repair of the structural congenital malformation. This study was aimed to compare the safety and efficacy of these drugs given in combination with flurbiprofen axetil as the postoperative analgesia in children. Children undergone the repair of structural congenital malformation in 9 centers were included in this study (n = 910). Patients were randomly grouped as: H1, hydromorphone 0.1 mg/kg; H2, hydromorphone 0.2 mg/kg; and C, sufentanil 1.5 $\mu$g/kg. All the patients also received 5 mg/kg diluted flurbiprofen axetil. Drugs were diluted to 100 mL by 0.9% saline and injected through intravenous electronic analgesic pump with background dose of 2 mL/h. Primary endpoint included the Face, Legs, Activity, Cry and Consolability (FLACC) score, while secondary endpoints had the Ramsay sedation score, heart rate (HR), respiration rate (RR), pulse oxygen saturation ($SpO_2$) and side-effects in 48 h of surgery. No significant differences in HR, $SpO_2$ and RR were observed among the groups in the period from post-anesthesia care unit (PACU) discharge to 48 h of discharge. However, the intergroup differences in FLACC score at the time of discharge from the PACU till 36 h later were statistically significant. FLACC score was lower in the H2 group compared to other two groups. Moreover, the adverse reactions were higher in group C compared to the other groups. These results depicted that hydromorphone hydrochloride 0.2 mg/kg and flurbiprofen axetil 5 mg/kg had better efficacy with fewer adverse effects than sufentanil 1.5 $\mu$g/kg with flurbiprofen axetil 5 mg/kg in the pediatric population undergone repair of the structural congenital malformation.

## Keywords

Hydromorphone; Postoperative analgesia; Pediatric; Sufentanil; Flurbiprofen axetil

## 1. Introduction

Around 5 million children undergo surgery every year in the United States, and almost half experience moderate to severe pain in the initial postoperative period [1]. Repair procedures of structural congenital malformations cause severe postoperative pain [2, 3], which may negatively affect children in ways such as growth difficulties, sleep disturbances, and behavioral changes [4]. Multiple studies have shown that postoperative pain control in pediatric patients is inadequate because of the adverse impact of opioid analgesics among other reasons [5, 6]. The optimal postoperative analgesic strategies for such patients are thus prioritized for research. There are few studies on postoperative analgesia in pediatric surgery. Optimal approaches for managing postoperative pain are not identified [7]. Clinicians are concerned that the opioids


  

usage in treating postoperative pain may affect the evaluation of neurological function in children, and complications like respiratory depression may arise [8].

Opioid analgesia is the most effective in moderating the severe pain. Opioids reduce pain scores after the surgery as found in adult studies [9]. Opioids are also used in the post-anesthesia care units (PACU) and wards as postoperative analgesia in pediatric surgery [10]. Hydromorphone being a semisynthetic $\mu$ and $\delta$ opioid agonist is popular regarding clinical practice in the USA and Europe because of robust analgesic efficacy, absence of analgesic ceiling effect, and fewer adverse effects compared to morphine [11]. In contrast, sufentanil being a selective $\mu$-receptor agonist and typical analgesic is used as pediatric postoperative analgesia in China due to rapid onset, powerful analgesic impact, and short half-life [12]. The data pertaining to efficacy and safety of sufentanil or hydromorphone in children undergone repair of structural congenital malformation are limited. Our previous study has demonstrated the benefits of hydromorphone as postoperative analgesia in children [13], however further research across more centers and larger sample size is required for better clinical evidence. Multi-center research trial can expand samples' representativeness and diversity for wider applicability of results. It can reduce deviation caused by regional differences. The collective results better guide about the clinical drug usage.

The primary aim of this prospective, randomized, multicentered and controlled trial was to compare the safety and efficacy of hydromorphone hydrochloride with those of sufentanil combined with flurbiprofen axetil as the postoperative analgesia in children scheduled for structural congenital malformation repair.

## 2. Methods

This study was conducted across 8 centers. A prospective, randomized, controlled and double-blinded clinical design was used in this study. Patients of 6 months to 3 years age having American Society of Anesthesiologists (ASA) physical status I and II were included. They were scheduled for the repair of structural congenital malformations such as cleft lip, cleft palate, or both, and hypospadias under the general anesthesia. All patients were newly enrolled in this study with no patient from our previous study.

The exclusion criteria were as follows: children or premature infants with corrected age of less than 6 months; severely obese patients; having severe sleep apnea syndrome and arrhythmia; apparent or possibly difficult airways before the operation; having hepatitis or renal dysfunction; history of abnormal anesthesia recovery; long-term chronic pain and analgesic usage; having mental and neurological diseases; and allergic reactions toward hydromorphone hydrochloride, flurbiprofen axetil, opioids or their components. First, the hospitals participating in the study were screened to check their ability in performing the appropriate pediatric surgery in specified time frame. A statistical analysis regarding the type and number of surgeries at each center was conducted after study completion where no statistical difference was found. Procedures were thus equally distributed across all centers.

A computer-generated randomization table was evolved for allotting patients to the hydromorphone hydrochloride 1 group (H1 group, n = 316), the hydromorphone hydrochloride 2 group (H2 group, n = 295), and the sufentanil control group (C group, n = 299). Patients in H1 group received hydromorphone hydrochloride 0.1 mg/kg, those in H2 group hydromorphone hydrochloride 0.2 mg/kg, and those in C group sufentanil 1.5 $\mu$g/kg, along with flurbiprofen axetil 5 mg/kg diluted in 100-mL intravenous analgesic pump in each group. Two doses of hydromorphone hydrochloride were tested to determine their efficacy for postoperative pain with least adversities. The selected doses were based on equivalent doses of two opioids and those of given in previous studies [13]. If morphine had analgesic intensity of 1, the hydromorphone would have 10 and sufentanil as 1000. Sufentanil was the standard care in our hospital and administered accordingly. Compared to 1.5 $\mu$g sufentanil, the equivalent hydromorphone hydrochloride dose was 0.15 mg, and thus, its two doses, *i.e.*, 0.1 mg and 0.2 mg were used in this study. The drugs solutions were prepared by medical staff not participating in the clinical observations to ensure double blinding. Moreover, the three drugs had same appearance. Drugs were diluted to 100 mL with 0.9% saline and injected to intravenous electronic analgesic pump with background dose of 2 mL/h and bolus-dose of 2 mL. It was limited to 10 mL/hour with 10-min lockout interval. The selected doses and analgesic pump parameters were based on the treatment routine of primary center and those of given in previous studies [13]. Infusion via the intravenous analgesic pump was ceased after 48 h of surgery.

Patients were sedated by intravenous administration of 1.0 mg/kg propofol before transferring to operating room. Electrocardiography (ECG), heart rate (HR), non-invasive blood pressure (BP), pulse oximetry, and end-tidal $CO_2$ levels were monitored during the operation. Anesthesia was induced by the intravenous administration of 0.2 mg/kg cisatracurium, 0.3 $\mu$g/kg sufentanil, and 2.5–3.0 mg/kg propofol. Endotracheal or laryngeal mask airway intubation was performed after 3 min followed by mechanical ventilation. Patients were given 2–3% sevoflurane for maintaining anesthesia. A bolus dose of sufentanil along with continuous intravenous propofol were administered to maintain the anesthesia depth. The muscle relaxation was achieved with bolus dose of cisatracurium. BP and HR were intraoperatively maintained within 20% of baseline values by administering vasoactive drugs. Sufentanil and cisatracurium were stopped 30 min before the end of operation, and 0.1 mg/kg tropisetron was intravenously injected. The intravenous analgesic pump was started 10 min before the end of surgery in each group. Sevoflurane and continuous infusion of medications was ceased at the end of procedure, and patients were transferred to the PACU. The tracheal tube or laryngeal mask airway was extubated upon the patient regaining consciousness and spontaneous breathing. Patients were monitored and received oxygen for minimum 30 min in the PACU. Patients' pain scores were recorded via the Face, Legs, Activity, Cry and Consolability (FLACC) scale during stay in the PACU [14]. The assessor pressed button on intravenous analgesic pump if score was more than 4. A 2-mL bolus was then administered as the rescue analgesia. Sufentanil 0.05 $\mu$g/kg was intravenously injected to the patients requiring

rescue analgesia more than twice. Drug was given at the 10 min intervals until patient's score was $\leq$4. Patients were not discharged from the PACU until their HR, BP and $SpO_2$ were monitored for minimum 20 min after each administration.

Postoperative pain in the ward was managed by a professional investigator in the Department of Anesthesiology. The type, time and dose of rescue analgesia were recorded. HR, BP and $SpO_2$ were monitored for minimum 8 h in the ward. FLACC score, HR, RR, $SpO_2$ and Ramsay sedation score were recorded for all three groups at leaving the PACU and 2, 6, 12, 24, 36 and 48 h after surgery [15]. The awakening time, FLACC score, and Ramsay sedation score were recorded after extubation. Furthermore, adverse reactions (nausea, vomiting, pruritus and abnormal bleeding), hospitalization cost, and length of stay were documented.

The main therapeutic index of this study was the postoperative pain score (FLACC score) of children. The hypothesis was that postoperative analgesic impact of hydromorphone was no worse than that of sufentanil. A 1:1 design was adopted for the trial and control groups with test parameter settings of unilateral $\alpha = 0.025$ and $1 - \beta = 90\%$. Difference in FLACC scores of the two drugs was 0.5 according to previous studies [13]. A total of 750 cases were required as per the sample size calculation formula for three mean comparisons. There were 250 cases each in the H1, H2 and C groups. It was determined that actual case numbers for H1, H2 and C groups should not be less than 295 cases as 15% cases could be lost in the clinical trial.

Analysis was made by the SAS statistical software (V9.4, SAS Institute Inc., Cary, NC, USA), and the significance level of non-efficacy test was 0.025 unilateral. Results were presented as mean $\pm$ standard deviation (SD). The data inconsistent with normal distribution were presented as median and quartile distance (M(Q)). Rank sum test compared the differences among three groups. Differences in indicators (FLACC score, Ramsay sedation score, HR, RR and $SpO_2$) among three groups were determined at different times by repeated analysis of variance (ANOVA). A pairwise comparison was made for statistically significant difference. Chi-squared test was used to study the differences in adverse reactions among three groups. Differences between the groups were statistically significant at $p < 0.05$.

## 3. Results

No significant intergroup differences regarding age, weight, anesthesia time, operation time, intraoperative bleeding, wake time, wake pain score, wake sedation score, agitation look-ahead score, gender, ASA classification, and anesthesia mode were found ($p > 0.05$), as shown in Tables 1 and 2.

**TABLE 1. Demographic data of the three groups.**

| | C group (n = 299) | H1 group (n = 316) | H2 group (n = 295) | $\chi^2$ | $p$ |
|---|---|---|---|---|---|
| Age (yr) | 2.00 (2.00) | 2.00 (1.71) | 2.00 (2.00) | 3.555 | 0.169 |
| Weight (kg) | 10.00 (3.70) | 10.65 (4.00) | 11.00 (4.00) | 1.293 | 0.524 |
| Gender | | | | | |
| Male | 220 (73.6) | 226 (71.5) | 211 (71.5) | 0.423 | 0.809 |
| Female | 79 (26.4) | 90 (28.5) | 84 (28.5) | | |
| ASA | | | | | |
| Grade I | 132 (44.1) | 159 (50.3) | 133 (45.1) | 2.749 | 0.253 |
| Grade II | 167 (55.9) | 157 (49.7) | 162 (54.9) | | |

*ASA: American Society of Anesthesiologists.*

**TABLE 2. Operative data of the three groups.**

| | C group (n = 299) | H1 group (n = 316) | H2 group (n = 295) | $\chi^2$ | $p$ |
|---|---|---|---|---|---|
| Anesthesia time (min) | 120.00 (90.00) | 100.00 (85.00) | 110.00 (92.00) | 5.527 | 0.063 |
| Operation time (min) | 85.00 (80.00) | 70.00 (75.00) | 86.00 (79.00) | 5.306 | 0.070 |
| Intraoperative bleeding (mL) | 5.00 (11.51) | 5.00 (24.37) | 5.00 (13.71) | 3.271 | 0.195 |
| Wake time (min) | 20.00 (18.58) | 20.00 (18.15) | 20.00 (19.15) | 0.445 | 0.801 |
| Wake pain score | 2.00 (1.00) | 2.00 (1.00) | 2.00 (1.00) | 2.709 | 0.258 |
| Wake sedation score | 2.48 (1.00) | 2.57 (1.00) | 2.57 (1.00) | 2.019 | 0.364 |
| Agitation look-ahead score | 8.13 (5.00) | 8.38 (6.00) | 9.00 (4.00) | 0.609 | 0.737 |
| Anesthesia mode | | | | | |
| General anesthesia | 283 (94.6) | 301 (95.3) | 288 (97.6) | 3.686 | 0.158 |
| General anesthesia + sacral anesthesia | 16 (5.4) | 15 (4.7) | 7 (2.4) | | |

No statistically significant differences among three groups in HR (A), $SpO_2$ (B) and RR (C) ($p > 0.05$) at the PACU discharge till 48 h were recorded (Fig. 1). The differences in time regarding HR and RR for H1, H2 and control groups were statistically significant ($p < 0.05$). None of the three drugs caused abnormal changes in the vital signs of children, and they were more stable over time in each group.

The FLACC scores of three groups decreased with time ($p < 0.05$) and were <4 (Fig. 2A), which suggested that two drugs controlled the children mild pain. The FLACC score of H2 group was lower than that of C at 2, 6, 12 and 36 h of surgery ($p < 0.05$), while that of H2 group was lower than that of H1 at leaving the PACU and 2, 6, 12 and 24 h of surgery ($p < 0.05$). These results demonstrated that hydromorphone 0.2 mg/kg had better analgesic impact. Differences among the groups regarding Ramsay scores at 2, 12 and 24 h were statistically significant ($p < 0.05$). Differences among H1, H2 and C groups were also statistically significant ($p < 0.05$). Moreover, the Ramsay scores were <4 (Fig. 2B), which suggested that two drugs did not cause excessive sedation in children.

The intergroup differences in incidence of adverse reactions at each time point were statistically significant ($p < 0.05$), as shown in Table 3. Comparison revealed that it was higher in C group compared to the other two groups ($p < 0.05$).

## 4. Discussion

Perception of pain in children is like that in adults. In the fetal period, spinal cord and brain form the myelin sheath having injury-stimulated nerve bundles, substance P, and receptors which can be detected in the dorsal horn of fetus spinal cord [16]. The children's response to pain is more intense. It results in strong physiological and biochemical changes, causes serious complications, suppresses immune system function, and prolongs recovery time [17]. Postoperative pain affects short-term prognosis and causes long-term behavioral changes after the recovery. Surgical correction is the primary treatment for structural birth defects or structural congenital malformations such as cleft lip, cleft palate or both, hypospadias, and imperforate anus. This is the first prospective, randomized, double-blinded controlled trial comparing the efficacy and safety of hydromorphone hydrochloride or sufentanil combined with flurbiprofen axetil as postoperative analgesia in pediatric population. It is preferred to avoid the influence of unknown factors on test results. Two doses of hydromorphone, *i.e.*, 0.1 mg/kg and 0.2 mg/kg are assessed in this study. Results show that hydromorphone administration (0.2 mg/kg) is associated with lower FLACC scores, especially 2 to 12 h after surgery, and better pain relief compared to sufentanil (1.5 $\mu$g/kg) at different times after surgery.

Continuous intravenous postoperative analgesia can be personalized regarding dosage. It facilitates the safe and reliable postoperative pain management via the regular pain evaluation and selection of appropriate analgesia methods according to patient condition. Studies have shown that usage of opioid continuous intravenous postoperative analgesia has good analgesic impact which does not increase the opioid-related side effects [7]. A study employed fentanyl patient-controlled intravenous analgesia along with midazolam after craniotomy, wherein pain score decreased, and 25% children had mild adverse reactions [6]. Moreover, study depicted that sufentanil-based patient controlled analgesia (PCA) could effectively and safely be used in children after major congenital structural malformation repair surgeries. These findings were consistent with the outcomes herein, except much larger sufentanil dose was used in the previous study (5 $\mu$g/kg) [18]. Yang *et al.* [19] reported that sufentanil and hydromorphone had similar analgesic impact in adult patients having elective laparoscopy or open radical surgery. Flurbiprofen axetil was administered by the surgeon or by patients via patient-controlled intravenous analgesia upon experiencing pain. The parenteral equivalence ratio of hydromorphone hydrochloride to morphine sulfate was 5:1, being lower than 6.7:1 as recommended by the American Pain Society (1992) and Agency for Health Care Policy and Research [20]. In contrast, the parenteral equivalence ratio of sufentanil to morphine sulfate was 1000:1. The ratio of sufentanil to hydromorphone hydrochloride could thus be estimated as 150:1–200:1. In current study, the potency ratio of C group (1.5 $\mu$g/kg) to H1 (0.1 mg/kg) was 150:1, and that of C group (1.5 $\mu$g/kg) to H2 (0.2 mg/kg) was 75:1, being consistent with those by Chang *et al.* [20]. The analgesic impact of sufentanil might thus be related to the mismatch in "equi-analgesic" strengths of opioid. Hydromorphone intravenous (IV)-patient-controlled anesthesia could improve mood, which was linked with the pain relief through anti-anxiolytic and anti-depressive effects of excited $\delta$-opioid receptors [19]. Furthermore, the rapid redistribution of sufentanil contributed to the shortened analgesia duration [21].

Children are in growth and development stage. Their psychological and physiological aspects are immature. The pathophysiological response for pain may be more intense. The pain and unpleasant experience can have long-term impact on the child [22]. Therefore, good and moderate sedation has role in assessing child's condition, and short-term and long-term prognosis. A previous retrospective study proposed that hydromorphone via PCA should be considered as first-line analgesic for pediatric pain management [23]. This was also supported by the present study. It was found in our previous randomized controlled trial (RCT) study at one center that hydromorphone hydrochloride was more effective than sufentanil for postoperative pain in pediatric patients undergoing surgical repair of structural congenital malformation [13]. Therefore, the present multicenter study was conducted with larger sample size of new patients to provide conclusive evidence and clinically relevant solutions. In this trial, the Ramsay score in H2 group was higher than those in other two groups. However, there was no statistical difference which can be related to larger dose of hydromorphone achieving sedation through $\delta$-opioid receptors in the central nervous system [24]. Flurbiprofen axetil decreased the opioids usage and reduced the emergence agitation and Ramsay sedation scores [25], thereby enhancing the analgesic impact of opioids like fentanyl or sufentanil [19]. It would thus be safer for intraoperative and postoperative analgesia in children.

Opioids showed multiple adversities including respiratory depression, postoperative nausea and vomiting (PONV), pruritus, and excessive sedation. Hydromorphone in previous

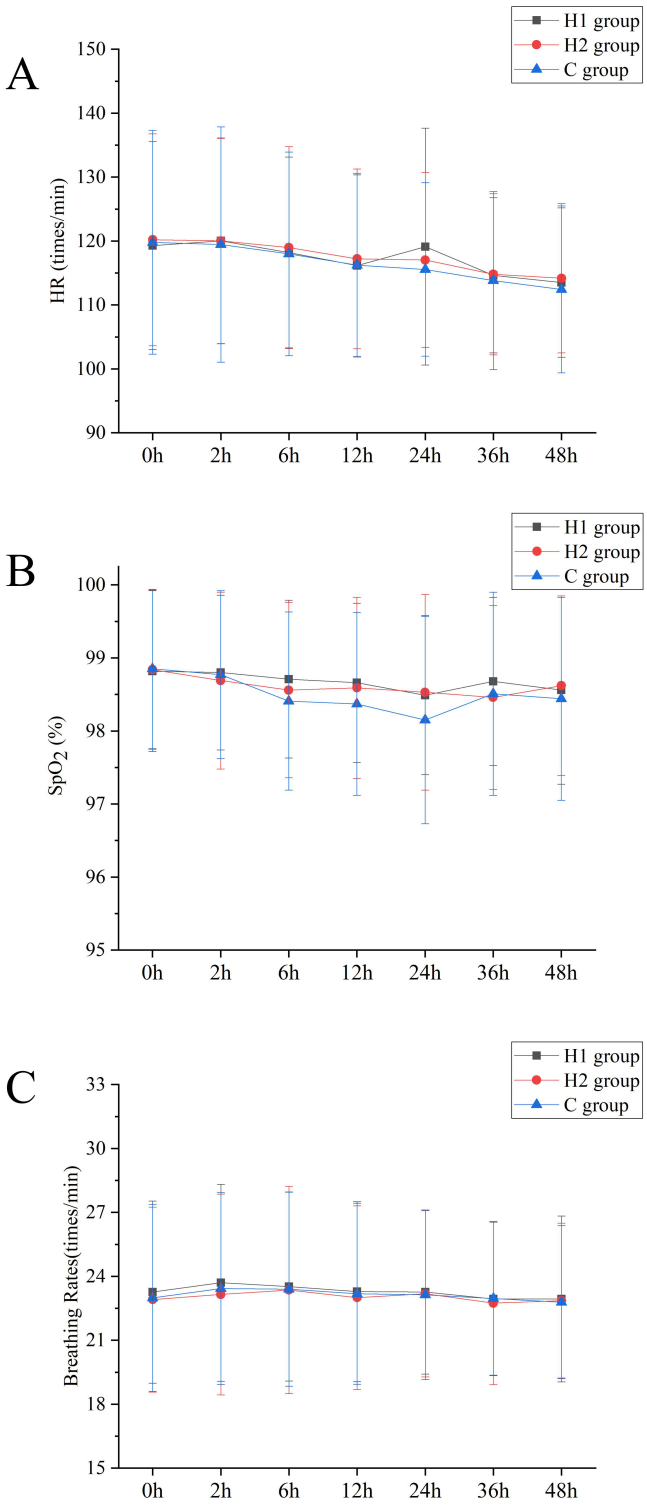


**FIGURE 1. Comparison of vital signs in three groups of children at different time points.** (A) The time main effect in heart rate comparisons was statistically significant ($f_{Time}$ = 25.580, $p_{Time} < 0.001$), and the group main effect was not statistically significant ($f_{Group}$ = 0.469, $p_{Group}$ = 0.626). The interaction between time and group was not statistically significant ($f_{Group \times Time}$ = 0.731, $p_{Group \times Time}$ = 0.554). (B) The time main effect in $SpO_2$ comparison was statistically significant ($f_{Time}$ = 5.365, $p_{Time}$ = 0.001), and the group main effect was not statistically significant ($f_{Group}$ = 1.147, $p_{Group}$ = 0.318). The interaction between time and group was not statistically significant ($f_{Group \times Time}$ = 0.786, $p_{Group \times Time}$ = 0.576). (C) The time main effect in comparing respiratory rates was statistically significant ($f_{Time}$ = 12.394, $p_{Time} < 0.001$), and the group main effect was not statistically significant ($f_{Group}$ = 0.322, $p_{Group}$ = 0.725). The interaction between time and group was not statistically significant ($f_{Group \times Time}$ = 0.732, $p_{Group \times Time}$ = 0.691). HR: heart rate; $SpO_2$: pulse oxygen saturation.

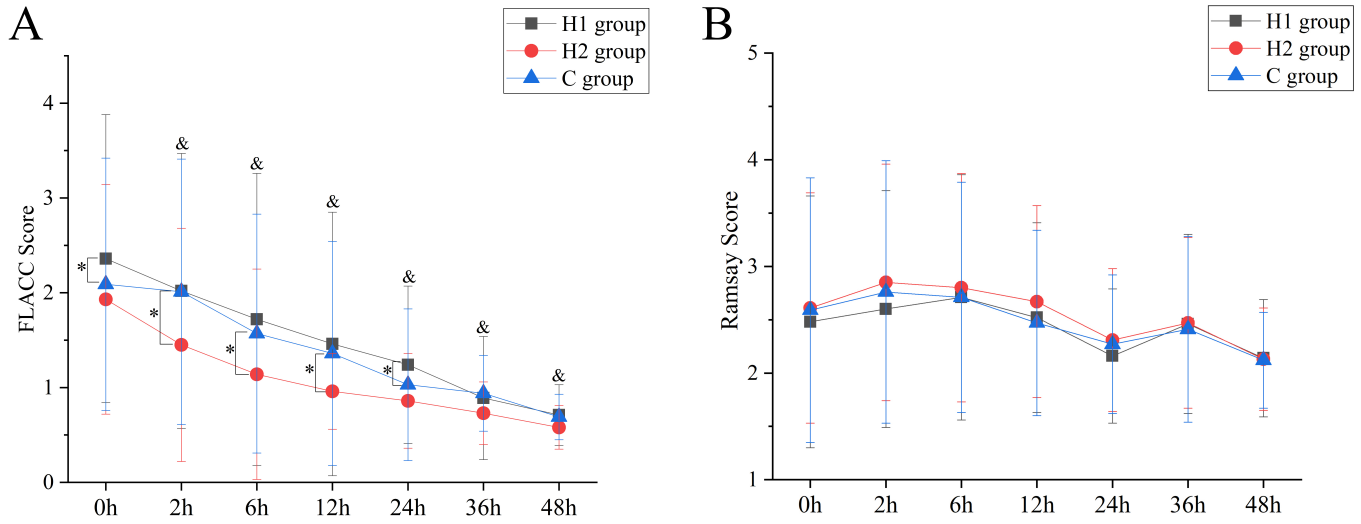


**FIGURE 2. Comparison of FLACC scores and Ramsay scores in three groups of children at different time points.** (A) The time main effect in comparing FLACC scores was statistically significant ($f_{Time} = 288.309$, $p_{Time} < 0.001$), and the group main effect was also statistically significant ($f_{Group} = 18.045$, $p_{Group} < 0.001$). The interaction between time and group was statistically significant ($f_{Group \times Time} = 4.414$, $p_{Group \times Time} < 0.001$). (B) The time main effect in comparing Ramsay scores was statistically significant ($f_{Time} = 81.499$, $p_{Time} < 0.001$), and the group main effect was not statistically significant ($f_{Group} = 2.789$, $p_{Group} = 0.062$). The interaction between time and group was not statistically significant ($f_{Group \times Time} = 1.617$, $p_{Group \times Time} = 0.107$). FLACC: Face, Legs, Activity, Cry and Consolability. *: compared with C group, $p < 0.05$; &: compared with 0 h, $p < 0.05$.

**TABLE 3. Incidence of adverse reactions in three groups at different time points (n (%)).**

| Adverse reactions | C group (n = 299) | H1 group (n = 316) | H2 group (n = 295) | $\chi^2$ | $p$ |
|---|---|---|---|---|---|
| At PACU discharge | | | | | |
| Absent | 284 (95.0) | 312 (98.7) | 293 (99.3) | 14.730 | 0.001 |
| Present (PONV) | 15 (5.0) | 4 (1.3)[a] | 2 (0.7)[a] | | |
| 2 h post-discharge | | | | | |
| Absent | 274 (91.6) | 305 (96.5) | 287 (97.3) | 12.229 | 0.002 |
| Present (PONV) | 25 (8.4) | 11 (3.5)[a] | 8 (2.7)[a] | | |
| 6 h post-discharge | | | | | |
| Absent | 257 (86.0) | 292 (92.4) | 273 (92.5) | 9.768 | 0.008 |
| Present (PONV) | 42 (14.0) | 24 (7.6)[a] | 22 (7.5)[a] | | |
| 12 h post-discharge | | | | | |
| Absent | 251 (83.9) | 290 (91.8) | 269 (91.2) | 11.731 | 0.003 |
| Present (PONV) | 48 (16.1) | 26 (8.2)[a] | 26 (8.8)[a] | | |
| 24 h post-discharge | | | | | |
| Absent | 258 (86.3) | 298 (94.3) | 274 (92.9) | 13.835 | 0.001 |
| Present (PONV) | 41 (13.7) | 18 (5.7)[a] | 21 (7.1)[a] | | |
| 36 h post-discharge | | | | | |
| Absent | 267 (89.3) | 299 (94.6) | 282 (95.6) | 10.837 | 0.004 |
| Present (PONV) | 32 (10.7) | 17 (5.4)[a] | 13 (4.4)[a] | | |
| 48 h post-discharge | | | | | |
| Absent | 275 (92.0) | 310 (98.1) | 285 (96.6) | 14.779 | 0.001 |
| Present (PONV) | 24 (8.0) | 6 (1.9)[a] | 10 (3.4)[a] | | |

*Note: [a]compared with C group, $p < 0.05$. PACU: post-anesthesia care unit; PONV: postoperative nausea and vomiting.*

studies had exhibited better pain control with fewer adverse effects. Rajan *et al*. [26] referred to it as the "clinical lore" compared with morphine. Results' comparison in present study showed that the PONV incidence in C group was higher than those in other two groups. This finding was consistent with the previous studies. PONV was caused by the factors such as anesthesia, operation mode, and the patient preoperative status [26]. No significant differences were found in this study regarding age, gender, weight, operation, surgery or anesthesia timing, anesthetics, and intraoperative opioid or other drugs. Furthermore, no differences in HR, RR and $SpO_2$ were recorded, which suggested that hydromorphone or sufentanil were safe as the postoperative analgesia. This study thus depicted that hydromorphone had better efficacy with fewer adverse effects. It could be a valuable choice for clinical use.

This study had certain limitations. Firstly, the applicability of this study was limited as opioids being restricted for postoperative analgesia in some countries. Secondly, the age of enrolled patients had reduced span of 6 months to 3 years, and results might not be applicable to other age ranges. Thirdly, all the patients underwent repair of structural congenital malformations, and results needed confirmation for the patients undergoing other types of surgeries. Lastly, various other dosages of sufentanil were not compared, which should be addressed in subsequent studies.

## 5. Conclusions

Based on the findings of this study, hydromorphone hydrochloride 0.2 mg/kg and flurbiprofen axetil 5 mg/kg had better efficacy with fewer adverse effects compared to sufentanil 1.5 $\mu$g/kg with flurbiprofen axetil 5 mg/kg in the pediatric population after repair of structural congenital malformation.

### ABBREVIATIONS

FLACC, Face, Legs, Activity, Cry and Consolability; HR, Heart rate; RR, Respiration rate; PACU, Post-anesthesia Care Unit; ASA, American Society of Anesthesiologists; ECG, Electrocardiography; BP, Blood pressure; SD, Standard deviation; ANOVA, One-way analysis of variance; PACU, post-anesthesia care unit; PONV, postoperative nausea and vomiting.

### AVAILABILITY OF DATA AND MATERIALS

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

### AUTHOR CONTRIBUTIONS

XGM, QRL, WQH, DQC, PL, DXL and YL—conceived and designed research. LGM, JJH, LJN, ZYY, TY, XG and XHC—collected data and conducted research. YYP—analyzed and interpreted data. BSZ—wrote the initial paper. XRS—had primary responsibility for final content. All authors read and approved the final manuscript.

### ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the Guangzhou Women and Children's Medical Center institutional review board (protocol No. 2017091701) and registered at ClinicalTrials.gov (registration No. ChiCTR-INR-17013935, http://www.chictr.org.cn/showproj.aspx?proj=23915, date of registration: 14 December 2017). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all individual participants included in the study.

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### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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