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Research Article

Adding Sufentanil to Ropivacaine in Pediatric Brachial Plexus Block Fails to Improve Analgesia: A Randomized Controlled Trial

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ABSTRACT

Background: Most studies have used sufentanil and ropivacaine for intrathecal anesthesia in adults or children, but few studies have used sufentanil and ropivacaine for peripheral nerve blocks, especially in children. The brachial plexus block is one of the most commonly used nerve block methods in children. Therefore, the purpose of this study was to investigate whether 0.1 μg/kg sufentanil combined with 0.25% ropivacaine can improve and prolong analgesia in children compared with ropivacaine alone.

Method: Eighty children, aged 5-10 years, undergoing upper limb surgery were randomly divided into two groups: the RS group (0.25% ropivacaine combined with 0.1 μg/kg sufentanil) and the R group (0.25% ropivacaine alone). The dosage of 0.25% ropivacaine administered to each group was 0.5 ml/kg. After general anesthesia, all children underwent ultrasound-guided brachial plexus block, which was performed by the same experienced anesthetist. The primary outcome measures were the Face, Legs, Activity, and Cry, Consolability Scale (FLACC) score at 2, 4, and 6 h after surgery and the duration of analgesia in each group. Secondary outcome measures were the changes in vital signs during surgery in each group, incidence of postoperative agitation, postoperative awake time, and duration of stay in the Post-Anesthesia Care Unit (PACU).

Results: The FLACC scores at 2, 4, and 6 hours after surgery and the duration of analgesia showed no statistically significant differences. There were no statistically significant differences in the changes in the vital signs during surgery between the groups. The incidence of postoperative agitation was significantly lower in the RS group than that in the R group (20% *vs*. 45%, $P<0.05$). A comparison of the postoperative awake time and duration of stay in the PACU showed no significant differences.

Conclusion: Compared with 0.25% ropivacaine alone, 0.1 μg/kg sufentanil combined with 0.25% ropivacaine for pediatric brachial plexus block did not improve analgesia or prolong analgesia, but it reduced postoperative agitation in children. The trial was registered with the Chinese Clinical Trial Registry (number: ChiCTR2000032071).

Keywords : Sufentanil; Brachial plexus; Nerve block; Pediatrics

ABBREVIATIONS

ASA: American Society of Anesthesiologists; FLACC: Face, Legs, Activity, Cry, Consolability Scale; PACU: Post-Anesthesia Care Unit; MHz: Megahertz; MAC: Minimum Alveolar Concentration; HR: Heart Rate; MAP: Mean Arterial Pressure SpO_2;: Pulse Oxygen Saturation; RR: Respiratory Rate; $PETCO_2$ End-tidal Carbon Dioxide Partial Pressure.

INTRODUCTION

With the development of ultrasound technology, the use of peripheral nerve blocks has become more common in thepediatric population.Even though ultrasound guidance could

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further reduce the risk of nerve injury, accidental entry into blood vessels, bleeding, and other factors, the concentration or dosage of local anesthetic drugs should be carefully selected because of the small diameter of nerve fibers, thin nerves, and short distance between adjacent Ranvier's nodes in children [1,2].

Therefore, prolonging the analgesic duration of nerve blocks has been widely studied. In clinical practice, the analgesic effect is often prolonged by continuous administration through peripheral nerve catheterization or by adding other drugs to local anesthetics. Due to difficulties with catheter care in the pediatric population with features such as poor cooperation and compliance and frequent adverse effects of peripheral nerve catheterization, the clinical use of catheterization is limited [3,4]. Previous studies have shown that dexamethasone or dexmedetomidine combined with local anesthetics can prolong analgesia, but the mechanism of action remains unclear [5,6].

With the discovery of peripheral opioid receptors, a large number of studies have shown that local anesthetics combined with opioids could improve the analgesic effect of regional blocks, prolong the duration of analgesia, and reduce the use of local anesthetics [7-9]. However, most of these studies used sufentanil and ropivacaine for intrathecal anesthesia in adults or children [10-12], and few studies have used sufentanil and ropivacaine for peripheral nerve blocks, especially in children. Brachial plexus block is one of the most commonly used nerve-block methods in children and is mainly used in upper-limb surgery by injecting local anesthesia around the brachial plexus [13]. Therefore, the purpose of this study was to investigate whether 0.1 μg/kg sufentanil combined with 0.25% ropivacaine can improve and prolong analgesia in children compared with ropivacaine alone.

MATERIALS AND METHODS

After obtaining approval from our Institutional Ethics Committee, the parents of each child read and signed an informed consent form before enrolment in the study. We studied 80 children, American Society of Anesthesiologists (ASA) physical status I, aged 5-10 years who were undergoing unilateral internal fixation for upper-limb fractures. Exclusion criteria were bilateral upper-limb surgery, history of allergy to local anesthetics, neuromuscular disease, and preoperative history of upper respiratory tract infection, coagulopathy, and communication difficulties. All children were randomly divided into two groups: the RS group (0.25% ropivacaine combined with 0.1 μg/kg sufentanil) and the R group (0.25% ropivacaine alone). The dosage of 0.25% ropivacaine administered to each group was 0.5 ml/kg. A randomization protocol was created by a specific investigator using random number generator software. Information about the groups to which the children were randomized was kept in prepared non-transparent envelopes. All patients, Post-Anesthesia Care Unit (PACU) nurses, and post-operative follow-up personnel were blinded to the group allocation.The patients were not administered premedication.

They were monitored using electrocardiography and pulse oximetry, and their blood pressure was measured non-invasively after arriving at the operating room. After an intravenous infusion of saline 0.9% was established, anesthesia was induced with propofol 2 mg/kg. When the patient lost consciousness, 6% sevoflurane was inhaled by mask, and the oxygen flow was adjusted to 5 L/min. After loss of eyelash reflex and jaw relaxation, a laryngeal mask was placed and fixed, preserving the patient's spontaneous breathing. Anesthesia was maintained using 3% sevoflurane. All patients underwent ultrasound-guided intermuscular groove brachial plexus block, which was performed by the same experienced anesthetist. A 5-10 MHz line-type ultrasound probe was selected to discern the target nerves and surrounding anatomy. The probe was placed above the clavicle, and the structures of the anterior medial scalenus and beaded brachial plexus were obtained on ultrasound images. A 21G puncture needle was inserted into the plane along the long axis of the probe. The drug was administered when the tip of the needle was close to the brachial plexus. No other opioids were used during the surgery. When the patient's plaster was fixed at the end of the procedure, sevoflurane was stopped and inhaled with oxygen at 5 L/min, and the laryngeal mask was removed. The patient was admitted to the PACU when the Minimum Alveolar Concentration (MAC) decreased to 0.6. During surgery, if the Heart Rate (HR) or Mean Arterial Pressure (MAP) increased by more than 20% of the baseline value, sevoflurane concentration could be increased to deepen anesthesia. Atropine 0.01 mg/kg or ephedrine 0.3 mg/kg was administered if the reduction of HR or MAP was greater than 20% of the baseline value. Postoperative agitation was assessed using the Ramsay Scale [14]. Sedation with propofol (1 mg/kg) and agitation occurred in the PACU. Postoperative pain was measured using the Face, Legs, Activity, Cry, Consolability scale (FLACC) score [15]. (Each item was scored from 0 to 2 points, with a total score of 10 points. 0, relatively comfortable; 1-3, mild discomfort; 4-6, moderate pain; 7-10, severe pain). If the score was greater than 4, treatment with 0.5 mg/kg ketorolac tromethamine was given.

The primary outcome measures were the FLACC scores at 2, 4, and 6 h after surgery and the duration of analgesia in each group. Secondary outcome measures were the changes in vital signs during surgery in each group, incidence of postoperative agitation, postoperative awake time, and duration of stay in the PACU. All adverse events were recorded. The sample size was calculated based on our preliminary experiment, which enrolled 10 patients in each group. The duration of analgesia was 341.7 ± 53.5 for the RS group and 307.4 ± 50.6 for the R group. Using the standard sample size calculation formula to achieve a power of 0.8 at α=0.05, there should be at least 36 patients included in each group to detect a significant difference. We planned to enroll 40 patients per study group to account for patient dropouts or missing data. Statistical analyses were performed using SPSS 18.0. Measurement data were expressed as mean ± standard deviation, and intergroup comparisons were used for group t-test. Count data were expressed as percentages, and the chi-square test was used for the comparison between groups. $P<0.05$ was considered statistically significant.

RESULTS

Eighty children were included in this study, and each group comprised 40 children. There were no between the two groups in terms of age, weight, sex, or duration of operation (Table 1).

Table 1: Patient demographics and perioperative data.

	RS Group (n=40)	R Group (n=40)	P-value
Age (years)	7.5 ± 1.2	7.5 ± 1.3	1
Weight (kg)	27.8 ± 5.1	25.6 ± 5.5	0.07
Sex (male/ female)	28/12	26/14	0.63
Duration of operation (min)	39.3 ± 8.1	40.5 ± 6.1	0.46

The effects of brachial plexus block in all children were perfect, and there was no need to increase the sevoflurane concentration during the operation. There were no statistically significant differences in MAP, HR, pulse oxygen saturation Point (SpO_2), Respiratory Rate (RR), end-tidal carbon dioxide partial pressure ($PETCO_2$), tidal volume, or end-expiratory sevoflurane and concentrations between the two groups after entering the operating room, anesthesia induction, or at the beginning of the operation (skin incision) (Tables 2-4).

Table 2: Comparison of vital signs after entering the operating room.

	RS Group (n=40)	R Group (n=40)	P-value
RR (/min)	17.9 ± 7.2	20.0 ± 5.3	0.14
MAP (mmHg)	83.7 ± 8.2	80.7 ± 7.7	0.1
HR (/min)	95.9 ± 13.9	94.2 ± 16.1	0.61
SpO_2 (%)	99.8 ± 0.4	99.5 ± 0.9	0.06

Table 3: Comparison of vital signs after anesthesia induction.

	RS Group (n=40)	R Group (n=40)	P-value
RR (/min)	26.1 ± 4.5	27.6 ± 5.9	0.2
Tidal Volume	111.8 ± 22.0	109.0 ± 24.8	0.59
End-expiratory sevoflurane concentrations (%)	2.3 ± 0.3	2.4 ± 0.3	0.14
$PETCO_2$ (mmHg)	57.6 ± 6.5	55.1 ± 6.0	0.08
MAP (mmHg)	53.6 ± 6.2	55.9 ± 7.0	0.12
HR (/min)	95.8 ± 13.1	101.1 ± 12.0	0.06
SpO_2 (%)	99.5 ± 0.2	99.6 ± 0.4	0.16

Table 4: Comparison of vital signs at the beginning of the operation.

	RS Group (n=40)	R Group (n=40)	P-value
RR (/min)	36.1 ± 6.3	34.5 ± 8.7	0.35
Tidal volume	100.2 ± 20.4	94.2 ± 20.6	0.19
End-expiratory sevoflurane concentrations (%)	2.6 ± 0.4	2.7 ± 0.3	0.21
$PETCO_2$ (mmHg)	46.2 ± 5.5	48.2 ± 6.0	0.12
MAP (mmHg)	58.6 ± 8.5	61.8 ± 7.6	0.08
HR (/min)	99.2 ± 11.4	103.2 ± 13.6	0.16
SpO_2 (%)	99.6 ± 0.4	99.5 ± 0.6	0.38

Comparison of the postoperative awake time, duration of stay in the PACU, and duration of analgesia showed no significant differences (Table 5).

Table 5: Comparison of postoperative conditions.

	Group (n=40)	R Group (n=40)	P-value
Postoperative awake Time (min)	23.2 ± 2.2	23.2 ± 2.1	1
The duration of stay in PACU (min)	30.1 ± 4.0	28.8 ± 3.6	0.13
Analgesia duration (min)	331.4 ± 51.1	326.9 ± 56.7	0.71

The FLACC scores at 2, 4, and 6 hours after surgery also showed no statistically significant differences (Table 6).

Table 6: Comparison of postoperative FLACC scores.

	RS Group (n=40)	R Group (n=40)	P value
Postoperative 2 h	0.3 ± 0.1	0.3 ± 0.1	1

Postoperative 4 h	0.8 ± 0.2	0.9 ± 0.3	0.08
Postoperative 6 h	2.2 ± 1.0	2.6 ± 1.3	0.13

The incidence of postoperative agitation was significantly lower in the RS group than that in the R group (20% *vs.* 45%, P<0.05). No adverse reactions such as respiratory depression, nausea, or vomiting occurred in either group.

DISCUSSION

Accumulating evidence suggests that the antinociceptive mechanism of peripherally applied opioids is mediated by the activation of opioid receptors on peripheral sensory neurons [16,17]. Peripheral opioid receptors are synthesized in the dorsal root ganglion and transported intraaxonally to peripheral sensory nerve endings [18]. In relation to tissue damage and initiation of inflammation, opioid receptors on peripheral sensory neurons are up regulated, including G-protein coupling signaling, and recycling, resulting in the inhibition of neuronal excitability and analgesia [8,18-22]. Studies of clinical models of inflammatory pain have indicated an analgesic effect of peripherally applied opioids, but the acute inflammatory response caused by surgery may not be sufficient for timely up regulation of peripheral opioid receptors [23]. Randomized controlled trials of peripheral opioids in intraoperative regional anesthesia or postoperative analgesia were systematically reviewed by Picard et al. in 1997, and the authors concluded that there was no clinically relevant peripheral analgesic effect of opioids in acute pain [24].

In our study, there were no significant differences in respiration, circulation, or end-expiratory sevoflurane concentrations between the two groups before and after surgery, indicating that the anesthesia effect of the two groups was similar and the effect of brachial plexus block was perfect. There were no significant differences in postoperative analgesic time or FLACC score between the two groups, indicating that 0.1 μg/kg sufentanil combined with 0.25% ropivacaine for pediatric brachial plexus block did not prolong the analgesic time or improve the analgesic effect. The difference between the two groups in the incidence of postoperative agitation was statistically significant. The difference shows that 0.1 μg/kg sufentanil was beneficial in reducing the occurrence of agitation during the awakening period of children, which is similar to the results of previous studies [25].

Sufentanil was used in this study because it is a common opioid widely used in regional blocks owing to its high lipid solubility [26]. However, current clinical studies on peripheral nerve block with sufentanil mainly focus on adults and are relatively rare in children [9,10,27,28]. There was no report on the dosage of sufentanil for brachial plexus block in children, and it had been reported in adult studies that the dosage of 0.2 μg/kg could prolong the analgesia time [29]. Therefore, considering the physiological characteristics of children and our previous experience with anesthesia, the dosage of sufentanil was selected as 0.1 μg/kg in this study.

The commonly used concentration of ropivacaine in children with peripheral nerve block is the 0.2% ~ 0.3%. Bosenberg et al. believed that 0.2% ropivacaine could achieve analgesia, whereas 0.3% ropivacaine would lead to a higher incidence of motor nerve block in children [30]. To meet the need for postoperative analgesia and to reduce motor nerve block, 0.25% ropivacaine was selected for peripheral nerve block in this study.

The present study had the following limitations. First, the method of postoperative pain assessment in children was single and could not evaluate the pain situation comprehensively. The two groups of children included both pre and post-school years, and the differences in cognitive levels were large. Only FLACC scores were selected to evaluate the children's postoperative pain, possibly reducing the assessment accuracy [31]. Second, the children were all treated with plaster immobilization postoperatively; therefore, they were only evaluated for analgesic efficacy, and motor nerve blocks were not evaluated in each group. Third, the peripheral effects of sufentanil could not be accurately assessed, because no comparison was made with the same dosage of sufentanil administered intravenously. Finally, the small sample size of this study could not obtain positive results, which requires further verification with a larger sample size.

CONCLUSION

Compared with 0.25% ropivacaine alone, 0.1 μg/kg sufentanil combined with 0.25% ropivacaine for pediatric brachial plexus block did not improve analgesia or prolong analgesia, but it reduced postoperative agitation in children. Future research work can continue to add other opioids to local anesthetics to observe the clinical effects of peripheral nerve block, and better research can provide mechanisms for perineural opioid activity by studying basic opioid receptors.

DATA AVAILABILITY

The data used to support the findings of this study have been included in this article.

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No funding was obtained for this study.

AUTHOR CONTRIBUTIONS

YN and JL conducted the study and wrote the manuscript. LQC and CCZ helped with patient recruitment, data collection, and data analysis. XWL conducted the study and helped analyze the

data. JL helped design the study and was a major contributor to writing the manuscript. All authors have read and approved the final manuscript.

ETHICAL APPROVAL

The study was approved by the Ethical Committee of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (Zhejiang, China) (Ref:2017-54), based on the Declaration of Helsinki. The parents of each child read and signed an informed consent form before enrolment in the study.

CONFLICT OF INTEREST

The authors declare no conflicts of interest regarding the contents of this article.

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