Original Article
Effect of different routes of administration on early cognitive function following inguinal hernia repair

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Abstract: Purpose: To analyze the effects of different routes of dexmedetomidine administration on early cognitive function following inguinal hernia repair. Methods: A total of 83 patients with pediatric inguinal hernias admitted to our hospital from January 2018 to October 2020 were divided into control group (CNG, n = 41) and observation group (OG, n = 42) by random number table. The OG was given 2 μg/kg of dexmedetomidine hydrochloride by intranasal administration, and the CNG was treated with 0.5 μg/kg of dexmedetomidine hydrochloride via intravenous (IV) infusion pump. The hemodynamics, condition of anesthesia, awakening, and safety were compared between the two groups. Results: Systolic blood pressure and oxygen saturation levels at T1 and T2 in the OG were not different from those in the CNG (P > 0.05), and heart rates in the OG were all higher than those in the CNG (P < 0.05). The incidence of emergence agitation during awakening was 4.76% in the OG, which was lower than 21.95% compared with the CNG (P < 0.05). Ramsay sedation scores at 15 and 30 min after awakening in the OG were higher than those in the CNG (P < 0.05). PAED scores in the OG were lower than those in the CNG (P < 0.05). Cognitive, language, and motor scores in the OG were higher than those in the CNG at 3 days after surgery (P < 0.05), and the incidence of cognitive dysfunction was 4.76% in the OG at 3 days after surgery, which was lower compared with 21.95% in the CNG (P < 0.05). Conclusion: Application of dexmedetomidine hydrochloride by intranasal administration or intravenous infusion before induction can ensure rapid postoperative awakening of the children without causing significant fluctuations in blood pressure and oxygen saturation, and both methods have a high safety profile. However, intranasal administration results in more satisfactory sedation, less postoperative agitation upon awakening, and reduces postoperative cognitive dysfunction.

Keywords: Pediatric hernia, surgery, dexmedetomidine, mode of administration, cognitive dysfunction, effects

Introduction

Hernia is a common problem in pediatric surgery, and surgery is the preferred treatment option for children diagnosed with hernia. With the advancement of the minimally invasive laparoscopic technology, laparoscopic inguinal hernia repair (TAPP) [1] is now widely used in the clinical treatment of pediatric hernia. TAPP is not only minimally invasive and requires a short operative time, but also allows the surgeon to examine groin areas and any defects in the hernia sites [2].

TAPP for pediatric hernia is often performed with sevoflurane or balanced anesthesia. However, evidence has demonstrated that the application of sevoflurane can easily lead to the development of postoperative delirium pediatric surgical anesthesia and early postoperative cognitive dysfunction [3]. In order to prevent postoperative cognitive dysfunction and ensure rapid postoperative recovery in children, other drugs, such as adrenoceptor agonists, should be used in combination with anesthesia [4]. Dexmedetomidine is a class of highly selective α2 adrenoceptor agonists, which not only has analgesic and sedative effects, but also exhibits anxiolytic effects [5]. In a previous study, the application of dexmedetomidine in pediatric surgical anesthesia showed no significant effect on hemodynamics, exerting sedation...
resembles natural sleep with high safety [6]. However, dexmedetomidine has been widely used in adult surgery, and there is a lack of unified standards regarding its use in pediatric surgery in terms of the mode of administration.

Intravenous administration and transnasal administration are the common routes of administration for dexmedetomidine in pediatric surgery, but there is no conclusion on which administration is more satisfactory. In this study, 83 children with inguinal hernias were enrolled to compare these two modes of administration.

Materials and methods

Clinical data

A total of 83 children inguinal hernias admitted to our hospital from January 2018 to October 2020 were divided into control group (CNG, n = 41) and observation group (OG, n = 42) by random number table. Inclusion criteria: patients admitted to department of pediatric surgery, received inguinal hernia repair, age < 12 years, American Society of Anesthesiologists (ASA) grade I or II, met the indications for surgery, their parents signed the consent form, and the study was approved by Ethics Committee of Ji’an Maternal and Child Health Care Hospital. Exclusion criteria: patients with comorbid asthma, comorbid other respiratory diseases, history of treatment with cranial surgery, history of previous traumatic brain injury, comorbid neurological diseases, allergy to the study drug; and patients with serious adverse events in the perioperative period were excluded.

Methods

After fasting from all solid foods for 6 hours and liquids for 2 hours, intravenous access was established. With the assistance of parents, the head of the child was kept slightly tilted back and the nasal cavity was kept below the oropharynx. The anesthesiologist slowly dripped the appropriate liquid into the bilateral nasal cavity, followed by several times of gentle pressure on the bilateral nasal flanks. In the CNG, 0.5 µg/kg of dexmedetomidine hydrochloride was injected intravenously within 10 min (specification: 2 mL: 200 µg, H20090248, Jiangsu Heng Swiss Medicine Co., Ltd.), and then 0.5 mL of normal saline was administrated into the nasal cavity. In the OG, 2 µg/kg of dexmedetomidine hydrochloride was diluted to 0.5 mL with saline and then dropped into the child’s nostrils bilaterally in equal amounts, followed by intravenous injection of 10 mL of saline within 10 min.

After completion of above operations, the children were transferred to the operating room to monitor the electrocardiogram (ECG), blood pressure, heart rate, axillary temperature and oxygen saturation. Induction of anesthesia was performed by intravenous injection of 0.4 µg/kg sufentanil (specification: 1 mL: 50 µg, H20054172, Yichang Renfu Pharmaceutical Co., Ltd.), 0.2 mg/kg etomidate (10 mL: 20 mg, H20083107, Zhejiang Jiuju Pharmaceutical Co. Ltd.), and 0.1 mg/kg cis-atracurium (10 mg, H20060869, Jiangsu Hengrui Pharmaceutical Co.). After successful induction, the laryngeal mask was placed for mechanical ventilation. Under pressure control mode, airway pressure was set at 9-12 cmH₂O, the respiratory rate was set at 18-25 breaths/min, and the partial pressure of end-expiratory carbon dioxide was set at about 40 mmHg. Intraoperative anesthesia was maintained by inhalation of 2%-3% sevoflurane (120 mL/bottle, H20070172, Shanghai Hengrui Pharmaceutical Co., Ltd.). 5% glucose injection was infused for intraoperative rehydration at 10 mL/kg per hour. Sevoflurane was discontinued upon completing the procedure and the child was transferred to Postanesthesia Care Unit (PACU), where the mask was removed when spontaneous breathing resumed with the tidal volume ≥ 8 mL/kg and the respiratory rate ≥ 16 breaths per minute. If no respiratory depression with normal blood pressure and heart rate were observed, the child could be transferred to the general ward.

Outcome measurement

The operation time, time to awakening (TTA), time for extubation of laryngeal mask airway (TLA), and PACU discharge time were compared between the two groups.

Hemodynamics: heart rate, systolic blood pressure, and oxygen saturation were measured in both groups at three time points: 10 min before surgery (T1), 10 min after beginning of surgery (T2), and at the end of surgery (T3).
Adverse reactions: the incidence of reduced oxygen saturation, bradycardia, respiratory depression, hypotension, nausea and vomiting was compared between the two groups.

Agitation upon awakening was assessed at 5 min, 15 min, and 30 min after awakening using pediatric anesthesia emergence delirium scale (PAED) [7], and Ramsay scores [8], respectively. The PAED scale was evaluated in terms of child being able to communicate with the caregiver, acting on instructions, being attentive to the surroundings, being irritable, and crying and unable to be soothed, which was evaluated as Not at all; Quite a bit; Very much; Extremely, with the first three as reverse scores and the last two as positive scores. A total score of > 10 indicated agitation. The Ramsay scale was rated 1-6, with 1: anxious or restless or both, 2: cooperative, orientated and tranquil, 3: responding to commands, 4: brisk response to stimulus, 5: sluggish response to stimulus and 6: no response to stimulus.

Cognitive dysfunction: BSID-III [9] was used for cognitive assessment 1 day preoperatively and 3 days postoperatively. It consists of three areas: cognitive, language (receptive language scale, expressive language scale), and motor (fine motor scale, gross motor scale). The cognitive dysfunction was diagnosed by Z-score method, and CNG was established for healthy individuals. The difference between the preoperative and postoperative scores of a single subtest minus the mean of the change in the CNG and divided by the standard deviation of the change in the CNG was the Z-score. An individual Z score of 1.96 or more was defined as cognitive dysfunction.

**Statistical methods**

Statistical analysis was performed with SPSS 23.0. Count data [n (%)] were examined by $X^2$ test. As for measurement data (X±s), inter-group comparisons were performed with independent samples t test, and intra-group comparisons were performed with paired t-test. Multi-point comparisons were analyzed by analysis of variance (ANOVA) with post hoc F test. Graphs were created with Graphpad Prism 8. $P < 0.05$ was considered statistically significant.

**Results**

**Baseline data**

There was no significant difference in baseline data such as gender, average age, average of body mass, ASA classification, and type of hernia between the two groups, which were comparable ($P > 0.05$) (Table 1).

**Surgical outcomes and hemodynamics**

The operation time, TTA, TLA, and PACU discharge time exhibited no statistically significant difference between the two groups ($P > 0.05$) (Figure 1). The heart rate, systolic blood pressure, and oxygen saturation levels did not differ significantly between the two groups ($P > 0.05$). However, the heart rate in the OG at T2 was higher than that in the CNG ($P < 0.05$). These indicators did not differ among T0, T1, and T2 within the OG ($P > 0.05$). The systolic blood pressure and oxygen saturation were not significantly different among T0, T1, and T2 in the CNG ($P > 0.05$), while the heart rate at T1 and T2 was significantly lower than the T0 ($P < 0.05$) (Figure 2).

<table>
<thead>
<tr>
<th>Data</th>
<th>Observation group (n = 42)</th>
<th>Control group (n = 41)</th>
<th>t/X²</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Gender</td>
<td>Male 30 (71.43)</td>
<td>32 (78.05)</td>
<td>0.481</td>
<td>0.488</td>
</tr>
<tr>
<td></td>
<td>Female 12 (28.57)</td>
<td>9 (21.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.38±2.16</td>
<td>6.51±2.34</td>
<td>0.263</td>
<td>0.793</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>21.39±4.18</td>
<td>22.13±4.52</td>
<td>0.775</td>
<td>0.441</td>
</tr>
<tr>
<td>ASA classification</td>
<td>I 22 (52.38)</td>
<td>24 (58.54)</td>
<td>0.318</td>
<td>0.573</td>
</tr>
<tr>
<td></td>
<td>II 20 (47.62)</td>
<td>17 (41.46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of hernia</td>
<td>Hiatal hernia 16 (38.10)</td>
<td>14 (34.15)</td>
<td>0.519</td>
<td>0.326</td>
</tr>
<tr>
<td></td>
<td>Umbilical hernia 20 (47.62)</td>
<td>22 (53.66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other 6 (14.29)</td>
<td>5 (12.20)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 1. Comparison of baseline data (X±s)/[n (%)]**
Adverse reactions

After medication, the OG had 1 case of bradycardia, 1 case of hypotension, and 2 cases of nausea and vomiting, with the incidence of adverse reactions of 9.52%; the CNG had 1 case of decreased oxygen saturation, 1 case of respiratory depression, 2 cases of hypotension, and 2 cases of nausea and vomiting, with the incidence of adverse reactions of 14.63%. The
incidence of adverse reactions did not differ significantly between the two groups ($P > 0.05$) (Table 2).

**Agitation during the awakening period**

The incidence of emergence agitation during awakening in the OG was 4.76%, which was significantly lower than 21.95% in the CNG ($X^2 = 3.942$, $P = 0.047$). No significant difference was observed in Ramsay sedation scores and PAED scores at 5 min after awakening ($P > 0.05$). Higher Ramsay sedation scores at 15 min and 30 min after awakening, and lower PAED scores were observed in the OG than in the CNG ($P < 0.05$) (Figure 3).

**Cognitive dysfunction**

The differences in cognitive, language, and motor scores in the BSID-III scale between the two groups on the preoperative 1 day were not significant, and they were higher in the OG than in the CNG on the postoperative 3 days ($P < 0.05$) (Figure 4). The incidence of cognitive dysfunction in the OG was 4.76%, which was lower than 21.95% in the CNG ($P < 0.05$) (Table 3).

**Discussion**

Laparoscopic hernia ligation in the treatment of pediatric hernia requires a short time and has a satisfactory outcome, and the common modalities of surgical anesthesia are balanced anesthesia with sevoflurane inhalation [10]. It has been found that pediatric patients, especially preschoolers, have a high likelihood in the development of impaired consciousness following sevoflurane anesthesia. Children are also prone to severe anxiety due to the fact that sevoflurane has an impact on EEG pattern and degradation products of sevoflurane, which may be an influential factor in the development of impaired consciousness after surgery [11]. Although the incidence of postoperative disorders of consciousness in pediatric patients is high, it is actually preventable, suggesting that good pain management and reasonable application of α2 agonists can inhibit the occurrence of postoperative disorders of consciousness [12].

Dexmedetomidine is a class of α2 adrenoceptor agonists with high selectivity, rapid onset of action after administration, short half-life,
simultaneous sedative and analgesic effects, without producing respiratory depression [13]. It was confirmed that the optimal dose of dexmedetomidine for intravenous infusion in children was 0.5 μg/kg [14], which was also the dose administered in the CNG. A study showed that dexmedetomidine could cause bradycardia and decreased blood pressure if the dose administered via nose exceeds 2.5 μg/kg [15], thus 2.0 μg/kg was given in the OG. The nasal mucosa is rich in capillaries, and administration by nasal drops ensures rapid entry of the drug into the bloodstream and less irritation to the nasal mucosa compared to other sedative drugs [16]. Dexmedetomidine penetrates via the sieve plate after intranasal administration, potentially preventing obstruction of the body’s blood-brain barrier under mechanisms of transcellular, paracellular, and active neuronal transport [17]. A previous study found that intranasal administration was more than 84% bioavailability in pediatric patients compared with the intramuscular and oral routes [18]. In this study, the systolic blood pressure and oxygen saturation levels of the OG at T0, T1 and T2 were not significantly different from those of the CNG, but heart rate at T1 and T2 was significantly higher than those of the CNG. The heart rate, systolic blood pressure and oxygen saturation levels of the OG at T0, T1 and T2 did not show significant fluctuations, while the heart rate at T1 and T2 of the CNG showed more significant fluctuations compared with that of T0. This indicated that intranasal administration of dexmedetomidine can alleviate heart rate fluctuations and maintain vital signs more effectively than intravenous administration during the perioperative period. Dexmedetomidine inhibits the sinus node, atrioventricular node, and interjunctional bundle, leading to a decrease in heart rate, but intranasal administration slows drug absorption, thereby preventing large fluctuations in hemodynamics [19].

It was shown that the frequent adverse reactions after dexmedetomidine application

### Table 3. Comparison of the incidence of cognitive dysfunction at 3 days after surgery [n (%)]

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Number of cases</th>
<th>Occurrence of cognitive dysfunction</th>
<th>No cognitive dysfunction occurred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>42</td>
<td>2 (4.76)</td>
<td>40 (95.24)</td>
</tr>
<tr>
<td>Control group</td>
<td>41</td>
<td>9 (21.95)</td>
<td>32 (78.05)</td>
</tr>
<tr>
<td>(X^2)</td>
<td>-</td>
<td>3.942</td>
<td></td>
</tr>
<tr>
<td>(P)</td>
<td>-</td>
<td>0.047</td>
<td></td>
</tr>
</tbody>
</table>

Figure 4. Comparison of BSID-III scale scores between the two groups. Cognitive (A), language (B), and motor (C) scores. *indicates \(P < 0.05\) compared with the control group.
 Analysis of different routes of administration in early cognitive function

included bradycardia, dry mouth, nausea, hypertension, and hypotension [20], and the total incidence of adverse reactions in this study was 9.52% in the OG, which was not significantly different from 14.63% in the CNG (P > 0.05). This indicates that dexmedetomidine has a high safety profile when applied before anesthesia in pediatric hernia repair, and that differences in the mode of administration do not have a serious impact on the safety of the drug. Intravenous administration of dexmedetomidine may cause transient hypertension and may also increase the incidence of bradycardia [21]. Agitation is a frequent postoperative complication in pediatric patients undergoing surgery and is influenced by various factors, such as personality, anesthetic modality, and preoperative anxiety level [22]. It was shown that the dexmedetomidine group had smoother perioperative hemodynamics and lower agitation scores compared with the CNG [23]. In this study, the incidence of agitation during the postoperative awakening period in the OG was lower than that in the CNG (4.76% vs. 21.95%), and the Ramsay sedation scores at 15 and 30 min after awakening were higher and the PAED scores were lower in the OG than in the CNG (P < 0.05). It indicates that dexmedetomidine administered by nasal drip ensures higher level of postoperative sedation and prevents the occurrence of agitation during the awakening period. A similar study also showed that the incidence of postoperative agitation was 4.8% in the OG with intranasal administration of dexmedetomidine, which was significantly lower than 47.6% in the CNG receiving fentanyl [24]. In another study, the children were given 0.5 μg/kg of dexmedetomidine hydrochloride by intravenous infusion and 1.5 μg/kg of dexmedetomidine hydrochloride by nasal administration 5 min before the end of surgery, respectively, and no significant difference in agitation scores and incidence of agitation was found between the two groups [25], which differed from the results of the present study, and may be caused by study subjects’ own conditions and differences in the dose of medication. In this study, the cognitive, language and motor scores in the BSID-III scale were higher in the OG than in the CNG 3 days after surgery, and the incidence of cognitive dysfunction was 4.76% in the OG 3 days after surgery, which was lower than 21.95% in the CNG (P < 0.05), suggesting that the administration of dexmedetomidine via noses can reduce the impact on the cognitive function in the early postoperative period, resulting in a better quality of recovery. The reason may be that dexmedetomidine can play an analgesic role along with sedation, and the child will not feel too much pain immediately after surgery [26].

In conclusion, both modes of administration ensure rapid postoperative awakening without causing significant fluctuations in blood pressure and oxygen saturation, and both modes have a high safety profile. However, intranasal administration can more significantly reduce heart rate fluctuations, decrease postoperative agitation and cognitive dysfunction during the awakening period, and maintain sedation effects. Nevertheless, only two groups were studied and the differences of the effects of different doses were not analyzed in this study, nor the differences in the mechanisms of action of intravenous and intranasal administration, which needs to be further investigated in future studies.

Disclosure of conflict of interest

None.

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References

Analysis of different routes of administration in early cognitive function


