Pharmacological analysis of dexmedetomidine hydrochloride in pediatric anesthesia during magnetic resonance imaging

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Abstract: Dexmendetomidine hydrochloride (DEX) is a new common adrenergic receptor agonist, which not only keeps children calm but also has analgesic effect. Dexmedetomidine hydrochloride will enable children to maintain the natural non-REM sleep, which can be stimulated sedation or language arousal. The aim of this study is to observe the sedative effect and adverse drug reactions of dexmedetomidine hydrochloride injection and propofol injection in MRI examination. In this study, no children in the experimental group were required to add sedative drugs, and 2 cases in the control group were treated with sedative drugs. In experimental group, it used dexmedetomidine hydrochloride as (1.64±0.91) g/kg; in control group, dosage of narcotic drugs as (5.26±1.82) g/kg, and the total complication rate of the children in the experimental group was lower than that of the control group ($P<0.05$). After returning to the ward, the doses of phenobarbital sedation were dexmedetomidine group (4.28±1.53) mg/kg and propofol group (6.40±1.71) mg/kg. There was significant difference between the two groups. The total complication rate in the experimental group was lower than that in the control group ($P<0.05$). The quality of MRI in the test group was significantly higher than that in the control group, which showed that dexmedetomidine hydrochloride could provide a satisfactory sedative effect in the MRI examination of children. To sum up, dexmedetomidine hydrochloride is a wide range of clinical applications. It is an effective drug for the maintenance of sedation in clinical disease treatment. It is flexible in the way of administration and with less adverse reactions. It is suitable for popularization and application in clinical practice.

Keywords: Dexmedetomidine, narcotic drugs, pediatric anesthesia, drug reaction, magnetic resonance examination.

INTRODUCTION

The sedative effect of dexmedetomidine hydrochloride simulates normal sleep, which can be awakened. It can be used for sedation during wake-up operation and less respiratory inhibition (Mei *et al.,* 2006). It is a popular sedation and anesthesia assistance, dexmedetomidine hydrochloride includes oral administration and nasal administration (Dubinsky *et al.,* 2004), subcutaneous injection, intramuscular injection and intravenous injection (Chin *et al.,* 2016). The peak time, the onset time and the peak concentration were quite different from each other. The drug had a biphasic half-life, the half-life of the distribution was about 6 min, and the elimination half-life was about 2h (Chen *et al.,* 2016). The individual differences in metabolic indices such as scavenging rate and half-life in the human body are smaller than that of dexmedetomidine hydrochloride. Research shows that the pharmacokinetic parameters showed no significant difference between different gender and age of the main drug dexmedetomidine hydrochloride (Damyanov *et al.,* 2015), dexmedetomidine hydrochloride is mainly in the liver metabolism, in order to reduce adverse reactions, it should be based on the function of liver and kidney and adjusting drug dose (Hertz *et al.,* 2016; Cirak *et al.,* 2015). Dexmedetomidine hydrochloride has various ways of drug use method, and has been applied in many clinical fields of children. Compared with other sedatives, it has many advantages, such as quick onset, less respiratory depression, repeated administration and less adverse reactions. It has a significant effect on reducing the agitation of children during general anesthesia recovery (Gazewood *et al.,* 2003). More and more children have received the treatment of dexmedetomidine hydrochloride, but lack of clinical experience. Further research is needed to monitor its efficacy and safety.

The analgesic effect of dexmedetomidine is complex. By means of intrathecal injection or epidural injection, $\alpha 2$ agonists do have analgesic effects (Liu *et al.,* 2017). Intrathecal injection of dexmedetomidine 1min can reduce blood pressure (Mei *et al.,* 2006; Chen *et al.,* 2016). When dexmedetomidine enters the epidural space, it can rapidly spread to cerebrospinal fluid. The effect of epidural on blood pressure was slower than intrathecal injection. Epidural medication was effective at 5 to 20min, and the basic site of analgesia was in the spinal cord (Damyanov *et al.,* 2015). Dexmedetomidin can reduce the need for anesthetics, and right metoimidine hydrochloride is used in ICU after surgery, which can reduce the need for 50% anesthetics compared with placebo (Antonova *et al.,*

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2015). Dexmedetomidine can reduce the pain of cold stimulation appropriately, and its analgesic effect is less than remifentanil. Incomplete cerebral ischemia-reperfusion animal models showed that dexmedetomidine reduced brain necrosis and improved neurological function. The rabbit model of focal cerebral ischemia confirmed that dexmedetomidine hydrochloride could reduce cortical neuron injury (Avci *et al.,* 2015). In the unilateral carotid artery ligation accompanied by a systemic hypotension model, the use of dexmeimidine hydrochloride can reduce the plasma concentration of catecholamine and reduce the damage of neuropathology and histopathology. It is generally believed that right dexmedetomidine hydrochloride reduces the outflow of catenol amine in brain and reduces brain tissue damage, apoptosis and apoptosis and brain protection. In addition, the decrease of excitatory glutamic acid in brain damage can also play a certain role in brain protection (Dezentje *et al.,* 2015).

Magnetic resonance imaging is a safe, reliable and noninvasive examination, because of its advantage is more and more children need for MRI (Ahmed *et al.,* 2016). Children do not have a good understanding and expression ability and poor self-control, not from the psychological, cognitive and environmental aspects of their communication (Liu *et al.,* 2017). Regular use of chloral hydrate or phenobarbital sedation, but due to individual differences in drugs, some children had difficulty in sedation (Antonova *et al.,* 2015; Avci *et al.,* 2015). At the same time, a part of children due to multiple sites examination or enhancement, the examination time was too long, resulting in repeated sedation and sedation difficulties, failed to complete the drug injection examination (Hertz *et al.,* 2016). Dexmendetomidine hydrochloride (DEX) is a new efficient α adrenergic receptor agonists are relatively common, not only can make the children stay calm, also has analgesic effect, and less influence on hemodynamics, but no inhibitory effect on respiration, less adverse reaction of the body to produce, can guarantee the safety of anesthesia (Dezentjé *et al.,* 2015; He *et al.,* 2015). Dexmedetomidine hydrochloride will enable children to maintain the natural non-REM sleep (NREM), and this kind of sedation can be stimulated or language arousal. The aim of this study is to observe the sedative effect and adverse drug reactions of dexmedetomidine hydrochloride injection and propofol injection in MRI examination in children.

MATERIALS AND METHODS

Research design

240 cases of children were selected and treated with 3.0TMRI in Qilu Hospital of Shandong University, China. This study was approved by the hospital ethics committee. All children's guardianship per person signed the informed consent. Diagnostic and admission criteria: Comply with the Guidelines for children's sedative monitoring and management of the American Academy of Pediatrics; American society of anesthesiologists (ASA) anesthesiology class I-II, age 1~6, body weight 6 ~ 23.5 kg, check the parts including the head, chest and abdomen and four limbs.

Exclusion criteria: Nearly 2 weeks of upper respiratory tract infection, severe heart, lung and nervous system disease, severe injuries, gastroesophageal reflux, airway obstruction, allergic to dexmedetomidine hydrochloride and propofol, predicted difficult airway, sleep apnea syndrome, nearly 1 months used sedative drugs.

Drugs: Dexmedetomidine hydrochloride injection, specification: 0.2mg/2mL, propofol injection, specification: 0.5g/50mL; compound lidocaine cream, specifications: 5%/10g, lidocaine hydrochloride injection, specifications: 0.1g/5ml, ephedrine hydrochloride injection, specifications: 30mg/1ml, atropine sulfate injection, specification: 0.5mg l

Restrictive conditions for drug use

Dexmedetomidine hydrochloride cannot enter the vein with blood and plasma in the same channel. The physical compatibility between them has not been confirmed. Dexmedetomidine hydrochloride cannot be used with amphotericin B or diazepam. Dexmedetomidine hydrochloride has been proved to be used simultaneously with the following liquids and drugs: 0.9% sodium chloride injection, 5% glucose injection, 20% mannitol injection, anfentanyl hydrochloride, lactic acid linger solution, fentanyl citrate, dexamethasone, aminophylline, digoxin, dihydrochloric acid, dopamine hydrochloride, dopamine hydrochloride, acid numbness, remifentanil, rocuronium, sodium bicarbonate, sodium nitroprusside, Si Kelin, sufentanil citrate, vecuronium and plasma substitutes.

Grouping and treatment

240 cases were randomly divided into 120 cases in the control group and 120 in the experimental group. All the children were forbidden to drink 2h before the medication. The children who were over 3 years old were forbidden to have solid food 8 h before giving medicine, and those who were less than 3 years old were 6h before giving the solid food and milk powder, without any preoperative medication. 0.5h before administration, local smear of compound lidocaine cream and 22G peripherally inserted cannula. In order to reduce the results of the injection of propofol, the 2 groups of patients were intravenously injected with 1% lidocaine hydrochloride (1mL). The control group intravenous loading dose of 2.5mg·kg^{-1} propofol injection, delivery time is 10min, then give a maintenance dose of 80 ~ 100 μg· kg^{-1}·min^{-1}, the test group of intravenous infusion of 1 μg· kg^{-1}.

Table 1: General data comparison

Variable	Control group (n=120)	Experimental group (n=120)
Gender (male/female)	32/28	31/29
Ae	3.18±2.45	3.43±2.67
Height	91.32±7.56	90.15±8.13
Weight	12.55±3.94	13.64±2.76
Body Mass Index	15.41±3.21	16.70±3.64
Heart rate	91.35±6.49	90.28±7.02
Systolic blood pressure	92.17±8.46	91.62±8.43
Diastolic blood pressure	59.13±5.21	58.56±6.13

Table 2: Changes of vital signs at each time point

Measurement variable	Group	T0	T1	T2	T3	T4
Heart rate	Experimental group (n=120)	109.2±14.2	79.8±10.2	84.3±10.9	86.7±11.5	108.3±11.7
	Control group (n=120)	115.3±13.8	103.3±11.5	95.6±10.8	101.2±9.5	109.5±11.3
Mean arterial pressure	Experimental group (n=120)	83.2±7.9	85.6±8.3	77.3±6.9	77.2±6.8	83.5±7.4
	Control group (n=120)	82.5±7.6	71.3±7.5	70.5±8.1	69.2±7.6	90.2±8.1
Respiratory rate	Experimental group (n=120)	25.3±3.9	24.1±3.2	24.5±3.6	24.8±4.0	25.4±3.8
	Control group (n=120)	24.1±3.8	21.6±4.0	19.6±3.1	22.4±4.2	25.3±5.0
Pulse oxygen saturation (Sp O_2)	Experimental group (n=120)	92.3±3.0	94.3±3.6	95.4±2.9	96.2±3.1	98.6±1.9
	Control group (n=120)	95.3±2.6	93.2±3.9	94.4±3.2	96.5±3.7	99.3±3.7

Table 3: Comparison of effect after anaesthesia

Effect after anaesthesia	Dosage of narcotic drugs (μg/kg)	Dose of Phenobarbital (mg/kg)
Experimental group(n=120)	1.64±0.91	4.28±1.53
Control group(n=120)	5.26±1.82	6.40±1.71
t value	6.9165	2.1648
P value	0.0000	0.0002

Table 4: Comparison of complications in two groups of children

Group	Respiratory depression	Hypotension	Restless	Nausea and vomiting	Total
Experimental group(n=120)	2(1.7%)	0(0%)	4(3.4%)	2(1.7%)	8(6.7%)
Control group(n=120)	14(11.7%)	6(5.0%)	6(5.0%)	2(1.7%)	28(23.3%)

Table 5: Analgesic effect

Group	Analgesic effect			
	Fully effective	Partial validity	Effective but adverse reactions	Invalid
Experimental group (n=120)	65	39	16	0
Control group (n=120)	42	22	56	0

Table 6: Magnetic resonance examination quality and inspection time

Variable	Experimental group (n=120)	Control group (n=120)
Check time (min)	23.4±5.8	28.2±7.1
Inspection quality		
Non body movement	108	84
Mild body movement	12	22
Large body movement	0	14

Observation index and evaluation of curative effect

After administration, the anesthesiologist with Ramsay sedation score, each of the 5 min assessment of a children's degree of sedation. When the children score reaches 5 points by the anesthesiologist escorted into the MRI room, with a padded properly fixed pediatric head and limbs, after checking into the next recovery room care until awake from anesthesia. After the administration of 15min if the Ramsay score did not reach 5 points, increase the drug dose group increased 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, the control group increased 10$\mu g \cdot kg^{-1} \cdot min^{-1}$, increase the dose after 3min if you have not reached 5 points, continue to increase the dose until the Ramsay score of 5. Midazolam 0.05$mg \cdot kg^{-1}$ injection was given if the somatic movement of children was detected during the examination. The calculation of the time for the onset of calming was from the beginning of the infusion to the Ramsay score of 5.

Before administration (T0), after administration of 10 min (T1), before beginning examination (T2), and after MRI examination, 5 min (T3) and children returned to ward (T4). The mean arterial pressure (MAP), heart rate (HR), pulse oxygen saturation (SpO_2) and respiratory frequency (RR) were recorded at these stages. The inspection process by close observation of pediatric anesthesiologists were face, lips and chest breathing, if the children were found to be less than 90% of SpO_2, the flow of oxygen was increased, and the treatment of the lower jaw was given. If it fails to improve, stop the examination, pressure the mask to oxygen and stop the infusion of drugs. If HR is less than 60 times$\cdot Min^{-1}$, give atropine 0.5 mg, MAP is less than 50 mm Hg, give ephedrine 6 mg.

After the examination of the quality and time of the MRI examination, the examination time was recorded and evaluated by the imaging physician. The quality of MRI examination is divided into 3 levels. 1 level: no movement in the whole process; 2 level: there is slight movement in the examination process, but it doesn't affect the inspection; 3 level: during the examination, there is a large body movement need to be re scanned.

STATISTICAL ANALYSIS

SPSS 16 software was used for statistical analysis. The measurement data is represented by means ± SD group compared with repeated measures ANOVA, compared with the single factor analysis of variance; count data rate (%), and $\chi 2$ test was used.

RESULTS

General information

There was no significant difference in the general data between the 2 groups (P>0.05) and table 1.

Comparison of the changes of vital signs

There was no significant difference in the MAP, HR and RR between the 2 groups before medication (P>0.05). Compared with T0, the MAP and HR in the experimental group decreased significantly in the T2-T3 stage, and the difference was statistically significant (P<0.05). T4 returned to the basal level. In the T1-T3 stage, MAP and HR in the control group were significantly lower than those in T0, the difference was statistically significant (P <0.05), and T4 returned to the basic level. In the T1-T3 phase, MAP and HR in the control group were significantly lower than those in the test group, (P<0.05), HR was significantly higher than that in the test group (P <0.05), the difference was statistically significant, and no drug treatment was given in the examination, see table 2.

Comparison of effect after anaesthesia

Dexmedetomidine in hydrochloride group were used dexmedetomidine hydrochloride in the maintenance of anesthesia (1.64±0.91) μg/kg; in control group, Dosage of narcotic drugs as (5.26±1.82) μg/kg, there were significant differences. Two groups of children back to the ward after using phenobarbital sedation dose of dexmedetomidine group (4.28±1.53mg/kg), propofol group (6.40±1.71) mg/kg. There are significant differences in the two groups, as shown in table 3. The total complication rate of the children in the experimental group was lower than that of the control group (P<0.05). See table 4. The analgesic effect is shown in table 5, the quality and time of examination of MRI were seen in table 6.

DISCUSSION

Propofol is a widely used sedative drug. It has the characteristics of quick effect and short time of action. It is commonly used in anesthesia induction, maintenance, sedation, and endoscopy (Dezentjé *et al.,* 2015). Propofol directly acts on synapses, promotes secretion of presynaptic membrane neurotransmitters, regulates membrane receptor activity, and plays an effective sedative effect (He *et al.,* 2015). Clinical studies have found that propofol may lead to a dose dependent respiratory depression in the patient, while the body is not fully developed in the child, the body's oxygen storage capacity is strong, and the transient respiratory depression is easily caused by hypoxemia, causing serious consequences (Chen *et al.,* 2016). Dexmedetomidine hydrochloride is a potent α2 receptor agonist. It has the effect of analgesic, anti sympathetic and so on. Studies have shown that dexmedetomidine also has the effect of maintaining hemodynamic stability, alleviating stress response and reducing restlessness in patients (Takahashi, 2017). The results showed that dexmedetomidine had the same sedative effect with propofol, but the former had little effect on the respiratory and circulatory system. Dexmedetomidin has a small impact on children's

respiration, and it can maintain a certain self-protection ability of the children's respiratory tract (Yazdi *et al.,* 2015). At the same time, the impact of the pump on the circulation system can be controlled in a small range by controlling the pump speed. Dexmedetomidine sedation is associated with inhibition of the locus coeruleus sympathetic adrenal medullary system. By activating the activity of the α2 receptor in the peripheral and central systems, it changes the conductivity of the ion channel, reduces the secretion of norepinephrine, inhibits the sympathetic activity, and causes bradycardia and hypotension (Wang *et al.,* 2016).

The main pharmacological effects of dexmedetomidine hydrochloride on respiration are a slight decrease in ventilation per minute and lower respiratory responsiveness at rest (Dubinsky *et al.,* 2004; Antonova *et al.,* 2015). The degree of inhibition of respiration than midazolam, propofol and opioid mild, can reduce midazolam and fentanyl, and opioid analgesic respiratory inhibition did not have synergistic effect, as well as for patients with severe respiratory disease patients (Dezentjé *et al.,*2015; He *et al.,* 2015). In the literature, we observed the changes of respiratory parameters after pediatric cardiac surgery (Mei *et al.,* 2006; Chen *et al.,* 2016). We found that dexmedetomidine hydrochloride could reduce tidal volume and reduce hypercapnia, but it had little clinical effect (Takahashi, 2017; Wang *et al.,* 2016). Dexmedetomidine hydrochloride dose and speed can affect the blood pressure, heart rate, cardiac output index of patients, the rapid infusion of dexmedetomidine hydrochloride, the drug has two-way regulating effect on blood pressure, medication should be avoided too quickly, for the patients with dexmedetomidine hydrochloride will happen dose dependent bradycardia. Research shows that when the input of small dose dexmedetomidine hydrochloride heart rate and blood pressure were decreased (Liu *et al.,* 2017), heart rate was significantly lower in pediatric patients will appear in the application of dexmedetomidine hydrochloride, so for patients with cardiovascular diseases in children, the drug should be used with caution (Wang *et al.,* 2003).

The onset time of dexmedetomidine hydrochloride in this experiment is about 16 min, longer than that reported in 8 min, which is related to the racial constitution difference and the low load dose used in this experiment. Dexmedetomidine hydrochloride adverse drug reaction is bradycardia and blood pressure reduction, but there are also studies suggesting that dexmedetomidine hydrochloride has no obvious effect on heart rate and blood pressure. In this study, although HR and MAP were lower than before, there was no clinical significance in the test group. Respiratory depression is a serious complication in the process of children's sedation, and experimental group account for 1.7% of the children's sedative complications, while control group account for 11.7% in this research.

Most children can not cooperate with MRI examination, need deep sedation coordination examination. At present, chloral hydrate has poor sedative effect. Benzene, two nitrogen drugs are prone to produce adverse drug reactions such as drug resistance, withdrawal and delirium (Li *et al.,* 2016). Therefore, it is urgent for us to screen a suitable sedative (Liu *et al.,* 2017). Dexmedetomidine hydrochloride is a new type of highly selective alpha 2 agonists, distribution half-life of 8 min, can direct effect on the central part of the locus coeruleus, induced sedation is similar to the natural sleep, which is characterized in that at the same time, sedation and analgesia can maintain the circulatory and respiratory smooth, safe for infants (Yazdi *et al.,* 2015). The most common in the children's MRI examination is the lack of sedation resulting in the failure of the examination or the impact of the imaging quality, and prolonging the time of the examination (Wang *et al.,* 2016). The experimental group in this study, children with no need for additional sedative drugs, control group had 2 cases, examination of additional sedative drugs, check the quality of the test group MRI was significantly higher than the control group, which indicates that the MRI examination for children dexmedetomidine hydrochloride can provide a satisfactory sedative effect (Antonova *et al.,* 2015; Avci *et al.,* 2015).

CONCLUSION

To sum up, dexmedetomidine hydrochloride has a wide range of clinical applications. It is an effective drug for the maintenance of sedation in clinical disease treatment. It is flexible in the way of administration and with less adverse reactions. It is suitable for popularization and application in clinical practice. In this study, the incidence of hypoxic saturation in the test group was significantly lower than that in the control group. This indicates that dexmedetomidine hydrochloride has less respiratory inhibition and higher safety. Therefore, dexmedetomidine hydrochloride can provide satisfactory sedation depth in children MRI examination, slight influence on respiration and circulation and low incidence of irritability in recovery period. It is an ideal choice for MRI examination in children.

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