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Comparison of Preoperative Sedation Effect of Dexmedetomidine Nasal Spray at Different Doses in Children with Cleft Palate

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Abstract

Purpose: To compare the preoperative sedation effect of dexmedetomidine nasal spray at different doses in children in order to obtain an ideal nasal spray dose.

Methods: 60 children with cleft palate repair (ASA I-II class) aged 1-3 years old were enrolled in this study in virtue of the randomized, double-blind, controlled study methods. They were randomly divided into 4 groups: dexmedetomidine nasal spray 2.0 μg/kg group (YM2.0 group), dexmedetomidine nasal spray 2.5 μg/kg group (YM2.5 group), dexmedetomidine nasal spray 3.0 μg/kg group (YM3.0 group), and normal saline nasal spray group (Con group). In YM2.0 group, YM2.5 group and YM3.0 group, aerosol nasal sprayer was used to spray nose. Dexmedetomidines 2.0 μg/kg, 2.5 μg/kg, and 3.0 μg/kg were given respectively. In Con group, normal saline was given by nasal sprayer. Heart rate (HR), oxygen saturation (Sp O2) and ramsay sedation scores were recorded at pre-dose (T0), 5 min (T1), 10 min (T2), 15 min (T3), 20 min (T4), 25 min (T5) and 30 min (T6), respectively. Time of falling asleep was recorded, crying was known when relative was separated from the children, as well as struggling during induction of inhalation, and awakening time after discontinuation of general anesthesia. Parental satisfaction was assessed by a modified children's parent satisfaction scale after surgery.

Results: After administrating dexmedetomidine 2.0 μg/kg, children fell asleep about 15 min, and after administrating dexmedetomidine 2.5 μg/kg and 3.0 μg/kg, children fell asleep about 10 min. Dexmedetomidines 2. 5 μg/kg and 3. 0 μg/kg ramsay sedation score at the same time point after falling asleep were higher than that of dexmedetomidine 2.0 μg/kg ($P < 0.05$). Most of the children who fell asleep after taking dexmedetomidine 2.0 μg/kg were awake and crying when they were separated from their relatives; most of the children who fell asleep after taking dexmedetomidines 2.5 μg/kg and 3.0 μg/kg were calm without waking up when they were separated from their relatives. Children who fell asleep after taking dexmedetomidine 2.0 μg/kg couldn't proceed sevoflurane induction silently; children who fell asleep after taking dexmedetomidines 2.5 μg/kg and 3.0 μg/kg could proceed sevoflurane induction silently so as to establish intravenous access. After discontinuation at the end of surgery, awakening time was longer with increasing dexmedetomidine dose; parental satisfaction was poor at dexmedetomidine 2.0 μg/kg, whereas parental satisfaction was satisfactory at dexmedetomidine 2.5 μg/kg; parents were slightly dissatisfied at dexmedetomidine 3.0 μg/kg. At dexmedetomidines 2.0 μg/kg, 2.5 μg/kg and 3.0 μg/kg, no serious complications such as low heart rate and respiratory depression were observed, and fewer adverse reactions such as crying reaction, bucking reaction and nausea and vomiting occurred during sedation.

Conclusion: Dexmedetomidine 2.5 μg/kg nasal spray is ideal for preoperative sedation, which can provide satisfactory sedation, less influence awakening, and better satisfy parents.

Keywords: Dexmedetomidine; Cleft palate repair; Pediatric; Sedation; Dose administered

1 Introduction

Pre-anesthesia sedation in children is difficult [1], traditional administration methods such as intramuscular injection, intravenous injection and

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and inhalation anesthetics are poorly accepted, children are difficult to cooperate, even causing psychological shadows in children[2], while as a new administration route, nasal spray has many advantages[3]: convenient for application, small pain for patients and easy to accept; abundant drugs for nasal mucosa blood supply are easy to be absorbed; it may not pass through enterohepatic circulation, the first-pass effect in the liver can be avoided and the bioavailability of the drug can be improved. Nasal spray is more easily absorbed than traditional nasal drip, and the bioavailability is higher. However, we found through preliminary test that the sedation effect of oral spray at 2.0μg/kg according to literature [4] is not ideal. Therefore, the ideal nasal spray dose of dexmedetomidine is explored through this study.

1.2 Study objects

All the children patients participated in the study were reviewed and approved by the Ethics Committee of the hospital, and the family signed the informed consent form.

A total of 60 children (ASA I-II class, aged 1-3 years old) with cleft palate repair who were hospitalized in our hospital from December 2017 to March 2019 were selected. Exclusion criteria: history of allergy to dexmedetomidine and severe hepatic and renal dysfunction. They were randomly divided into 4 groups: dexmedetomidine nasal spray 2.0 μg/kg group (YM2.0 group), dexmedetomidine nasal spray 2.5 μg/kg group (YM2.5 group), dexmedetomidine nasal spray 3.0 μg/kg group (YM3.0 group), and normal saline nasal spray group (Con group). In YM2.0 group, YM2.5 group and YM3.0 group, aerosol nasal sprayer was used to spray nose. Dexmedetomidines 2.0 μg/kg, 2.5 μg/kg, and 3.0 μg/kg were given respectively. In Con group, normal saline was given by nasal sprayer.

2 Methods

2.1 Pre-sedation evaluation

Anesthetic evaluation: The children patients should be fully evaluated by the anesthesiologist before sedation for the indications of sedation and the risks of sedation, and the parents should be informed of the possible risks of sedation, etc., and the informed consent form should be signed with the parents. Nursing evaluation: Whether the children patients have other symptoms other than this disease, what are the time of last eating, the amount of food intake, the time of sleep deprivation, and the sedation plan to be taken.

Strictly adhere to fasting requirements prior to sedation, confirm and record the final food and fluid intake and timing, and learn about any abnormalities prior to treatment.

The nurse evaluated and found that the children patients had eaten within the specified fasting time or the children patients had non-current examination diseases, and timely informed the anesthesiologist, so as to determine whether further medication of sedation or delayed medication of sedation could be used.

2. 2 Sedation implementations

For all children included in the study, dexmedetomidine hydrochloride (Yangtze River Pharmaceutical Group Co., Ltd.) bulk solution was used in accordance with 2.0 μg/kg, 2.5 μg/kg and 3.0 μg/kg, and intranasal spray administration was performed at normal saline, and the children patients were placed in sitting position, with head tilted forward, and dexmedetomidine or normal saline was slowly and uniformly sprayed into both nostrils in divided fractions. The spray equipment was aerosol nasal sprayer (model: M AD140, batch No.:170147, Wolfe Tory M edical, Inc).

All procedures were performed by the same nurse skilled in pediatric nasal administration techniques.

2.3 Anesthesia implementation:

All children patients were admitted into the operating room carrying by the nurses 30 min after nasal spray, given 8% sevoflurane to face mask, changed to 2% sevoflurane after full sedation, then established intravenous access, fentanyl 3 μg/kg, propofol 2 mg/kg, cis-atracurium 0.15 mg/kg, tracheal intubation after full muscle relaxation, propofol 4 mg/kg*h and remifentanil 0.4 μg/kg*min during surgery, and intermittent addition of cis-atracurium for maintenance of anesthesia. According to BIS value during operation, the dose of propofol and remifentanil (the BIS value was maintained between 40 and 60) was increased or decreased. Half an hour before the end of operation, cis-atracurium was discontinued. Propofol and remifentanil were discontinued at the end of operation. Tracheal catheter was removed when the patients regained consciousness and the tidal volume reached 8 ml/kg. After observation for 15 min, oxygen saturation was maintained at more than 95% and then the patients could be returned to the ward.

2.4 Monitoring indicators

Heart rate (HR), oxygen saturation (Sp O2) and ramsay sedation score (1 is under sedation, 2-4 is

adequate sedation and 5-6 is excessive sedation) of children patients were observed at pre-dose (T0) and 5 min (T1), 10 min (T2), 15 min (T3), 20 min (T4), 25 min (T5) and 30 min (T6), respectively. The time to falling asleep after intranasal administration of dexmedetomidine (time to ramsay sedation score of 3 after administration) was recorded; the condition of crying was known at the time of separation from the relatives of the children, as well as struggling at the time of inhalation induction and the awakening time after drug discontinuation. After the operation, the parent satisfaction scale [4] was modified to evaluate the overall satisfaction of the children's parents with the course of sedation in the form of questionnaire. 3 points for each item, the scoring grades are obtained according to the questionnaire, 7-9 points are satisfactory, 4-6 points are general and 0-3 points are unsatisfactory. The occurrence of crying reaction, bucking reaction, respiratory depression and nausea and vomiting during the whole nasal administration in sedation implementation were recorded. Among them, the children patients with cyanosis or Sp O2 < 90% were considered as respiratory depression.

2.5 Statistical treatment

SPSS 18.0 statistical software was used to analyze the data. The measurement data are expressed as ˋX±s. One-way analysis of variance or repeated measures analysis of variance were used for comparison, and χ^2 test was used for comparison of counting data. $P < 0.05$ was statistically significant.

3 Results

3.1 There was no significant difference in age, sex and weight of children patients between the 4 groups ($P > 0.05$). See Table 1

Table 1. **Comparison of General Conditions of Children Patients before Operation (x±s)**

Group	YM2.0	YM2.5	YM3.0	CON
Age (years old)	2.11±0.62	2.05±0.71	2.17±0.53	1.92±1.83
Sex Male/female	7/8	8/7	9/6	7/8
Weight (Kg)	14.73±1.22	14.53±1.58	14.92±1.73	14.26±1.89

3.2 Repeated measures analysis of variance was used, time factor:

F = 662.99, $P < 0.0001$, showing significant differences in sedation scores over time in the same group; group factor: F = 1094.45, $P < 0.0001$, indicating significant differences in sedation scores between groups at the same time point; time factor * group factor: F = 89.32, $P < 0.0001$, indicating that sedation scores varied with time between groups. Using Bonferroni posttests, the sedation scores of YM2.0 group, YM2.5 group and YM3.0 group were significantly higher than those of CON group after 10 min ($P < 0.001$). At 10 min, the sedation scores of YM2.5 group and YM3.0 group were significantly higher than that of YM2.0 group ($P < 0.001$), there was no significant difference in sedation scores between the three groups at 15 min ($P > 0.05$), and there was no significant difference between YM2.5 group and YM3.0 group at each time point ($P > 0.05$). See Table 2

Table 2. **Comparison of Ramsay Sedation Scores of 4 Groups of Children Patients at Different Time Points (x±s)**

Time point	T0	T1	T2	T3	T4	T5	T6
YM2.0	1.00±0.00	1.00±0.00	1.33±0.47	2.80±0.40	2.93±0.25	3.07±0.25	3.13±0.34
YM2.5	1.00±0.00	1.00±0.00	2.87±0.50	2.93±0.25	3.73±0.44	3.93±0.25	4.07±0.25
YM3.0	1.00±0.00	1.13±0.34	2.93±0.25	3.13±0.34	3.87±0.34	4.06±0.25	4.27±0.44
CON	1.00±0.00	1.00±0.00	1.00±0.00	1.00±0.00	1.00±0.00	1.00±0.00	1.00±0.00

3.3 Using repeated measures analysis of variance, time factor: F = 40.32, $P < 0.0001$, indicating that there was significant difference in the change of oxygen saturation with time in the same group; group factor: F = 40.40, $P < 0.0001$, indicating that there was significant difference in oxygen saturation between different groups at the same time point; time factor * group factor: F = 3.78, $P < 0.0001$, indicating that oxygen saturation trends varied over time between groups. Using Bonferroni posttests, compared with CON group, the oxygen saturation of YM2.0 group, YM2.5 group and YM3.0 group decreased significantly 15 min after administration ($P < 0.05$), but this was not clinically significant and did not cause hypoxia and respiratory depression.

Table 3. **Oxygen Saturation of 4 Groups of Children Patients at Different Time Points (x±s)**

Time point	T0	T1	T2	T3	T4	T5	T6
YM2.0	98.13±0.51	98.07±0.59	98.00±0.65	96.87±0.91	96.80±0.86	96.53±0.72	96.27±0.70
YM2.5	98.20±0.56	97.93±0.45	97.87±0.64	96.73±0.88	96.60±0.74	96.47±0.74	96.26±0.80
YM3.0	98.33±0.49	97.93±0.59	97.73±0.70	96.93±0.88	96.73±0.70	96.47±0.64	96.20±0.68
CON	98.33±0.61	98.20±0.56	98.13±0.52	98.13±0.99	97.73±0.96	97.87±1.13	98.33±1.29

3.4 Repeated measures analysis of variance was used, time factor: F = 123.89, P < 0. 0001, indicating that there was significant difference in heart rate changing with time in the same group; group factor: F = 279.85, *P* < 0. 0001, indicating that there was significant difference in heart rate between different groups at the same time point; time factor * group factor: F = 16.15, *P* < 0. 0001, indicating that heart rate trends varied over time between groups. Using Bonferroni posttests, compared with CON group, the heart rate of YM2.0 group decreased significantly after 10 min of administration, and the heart rate of YM2.5 group and YM3.0 group decreased significantly after 5 min of administration (*P* < 0.05).

Table 4. **Heart Rate of 4 Groups of Children Patients at Different Time Points (x±s)**

Time point	T0	T1	T2	T3	T4	T5	T6
YM2.0	134.47±10.93	134.20±4.87	120.80±5.39	112.93±7.43	105.27±7.52	105.29±5.14	103.00±4.72
YM2.5	135.60±8.20	127.20±7.76	114.93±6.76	103.93±6.41	104.40±6.20	104.93±6.88	99.27±4.46
YM3.0	133.60±8.45	123.47±6.50	111.80±6.83	99.93±4.36	97.87±4.16	97.53±3.14	95.67±3.40
CON	134.47±11.31	135.60±8.48	133.60±8.75	135.40±7.94	136.67±8.92	134.80±7.15	136.13±8.46

3.5 The time of falling asleep after nasal spray was analyzed by one-way analysis of variance, F = 50.29, *P* < 0. 0001 showed that there were significant differences in sleeping time between different groups. Bonferroni's Multiple Comparison Test was used between the two groups. The children patients in the control group did not sleep, and the children patients in YM2.5 group and YM3.0 group had significantly shorter sleeping time (*P* < 0. 001) compared with YM2.0 group, YM2.5 group and YM3.0 group after sedation. There was no significant difference in the time of falling asleep between YM2.5 group and YM3.0 group (*P* > 0.05).

One-way analysis of variance was used for awakening time of anesthesia, F = 22.86, *P* < 0. 0001 showed that there was significant difference in awakening time after anesthesia between different groups. Bonferroni's Multiple Comparison Test was used between the two groups. There was no significant difference in awakening time between YM2.0 group and CON group (*P* > 0.05). There was significant difference between the other two groups (*P* < 0. 05).

One-way analysis of variance was used for parent satisfaction scoring, F = 45.65, *P* < 0. 0001 showed that there were significant differences in parent satisfaction scores between the two groups. Bonferroni's Multiple Comparison Test was used for two groups, there were significant differences (P < 0. 05) in parent satisfaction scores between YM2.0 group, YM2.5 group and YM3.0 group compared with CON group. There was significant difference (*P* < 0. 05 and *P* ＜ 0. 01) between YM2.5 group, YM3.0 group and YM2.0 group. There was no significant difference between YM2.0 group and YM3.0 group (*P* > 0. 05).

Table 5. **Time to Fall Asleep after Nasal Spray, Awakening Time of Anesthesia and Parent Satisfaction Score (x±s) of 4 Groups**

Group	YM2.0	YM2.5	YM3.0	CON
Time to fall after nasal spray	16.00±2.00	10.67±1.70	10.33±1.25	No falling asleep
Awakening time of anesthesia	12.30±2.12	15.01±2.03	18.60.53±3.14	9.13±1.86
Parent satisfaction score	5.40±1.12	7.40±1.12	6.07±0.98	2.93±1.22

3.6 Chi square test was used, X^2 = 46.607, *P* < 0. 001, there was significant difference in sedation between different groups. There was no statistical difference between YM2.5 group and YM3.0 group and between YM2.0 group and CON group (P > 0. 05), i.e., YM2.5 group and YM3.0 group were quiet at inhalation induction, while YM2.0 group and CON group were not quiet at inhalation induction.

Table 6. **Sedation during Inhalation Induction in 4 Groups of Children Patients (Number Ratio)**

Group	YM2.0	YM2.5	YM3.0	CON
Quiet / struggling	3/12	14/1	15/0	0/15

3.7 Chi square test was used. Among the adverse reactions, crying / cooperating $X^2 = 2.069$, $P = 0.558$; bucking / normal $X^2 = 2.143$, $P = 0.543$; nausea and vomiting / none $X^2 = 3.051$, $P = 0.384$. There was no significant difference in the adverse reactions between the groups in the course of sedation ($P > 0.05$). There were few adverse reactions in each group.

Table 6. **Adverse Reactions during Sedation in 4 Groups of Children Patients (Number Ratio)**

Group	YM2.0	YM2.5	YM3.0	CON
Crying / cooperating	1/14	0/15	1/14	0/15
Bucking / normal	1/14	0/15	2/13	1/14
Nausea and vomiting / none	0/15	1/14	0/15	0/15

4 Discussion

The study showed [5] that the postoperative long-term psychological trauma may be caused by forced admission into the operating room. Rough general anesthesia induction, such as forced inhalation anesthesia induction, may cause about 17% -57% of pediatric personality and behavior changes, accompanied by increased sleepwalks, nocturia, and irritability, etc. In addition, noxious stimulation such as preoperative intramuscular injection and indwelling intravenous indwelling needle may also cause long-term phobia of children, afraid of people wearing white coat, green coat and mask, causing psychological trauma to the children patients. Therefore, seeking a non-invasive, comfortable, safe, and effective method of sedation is of great importance in pediatric comfort medical treatment.

Nasal administration is a central nervous system administration that can effectively avoid blood-brain barrier and first-pass effect, etc. It has the characteristics of non-invasive, rapid, convenient, no first-pass effect and high bioavailability, and it can reduce serious systemic adverse reactions. Dexmedetomidine is a highly selective α2 adrenoceptor agonist, which exerts sedative effect by highly selective agonist α2 adrenoceptors on the locus coeruleus [6]. Dexmedetomidine has been shown to produce safe and effective sedation when administered intranasally, K. INTHAVONG et al. [7] compared the deposition and removal of quantitative nasal spray and nasal dripping agent, with nasal spray deposited in the anterior part, a small portion of which is slowly cleared from the nasal mucosa cilia and transported to the nasopharynx, in contrast, the nasal dripping agent is mostly deposited in the posterior part, and mostly rapidly cleared to the nasopharynx, so that nasal spray has a faster absorption and high bioavailability than nasal dripping agent. Therefore, the use of nasal spray for dexmedetomidine can be an ideal method for preoperative sedation in children patients.

A number of literatures reported that [4][8][9][10], the intranasal administration of dexmedetomidine 2.0 μg/kg produced effective sedative effect. However, we found through preliminary test that although the nasal spray administration of 2.0 μg/kg caused sleep effect, the sedation was mild. When children patients were separated from their parents, they woke up again, it did not achieve the desired sedation effect, the sedation had a long onset time, and they usually went into sleep state after 15 min. Literature show that [11] the intranasal administration of dexmedetomidine was safe and effective up to 3.0 μg/kg, so this experiment used three doses of 2.0 μg/kg, 2.5 μg/kg and 3.0 μg/kg respectively, in order to find the most appropriate dose to be administered.

The results of this study indicate that children patients went into sleep state about 10 min at dexmedetomidines 2.5 μg/kg and 3.0 μg/kg. Relative to 2.0 μg/kg, there was significant difference. There was no significant difference in time to sleep dexmedetomidines 2.5 μg/kg and 3.0 μg/kg. After sleep, the children patients were given dexmedetomidines 2.5 μg/kg and 3.0 μg/kg at the same time point, BIS values were lower than dexmedetomidine 2.0 μg/kg ($P < 0.05$), and the ramsay sedation score was higher than dexmedetomidine 2.0 μg/kg ($P < 0.05$). Most of the children patients who fell asleep were awake and crying when they were separated from their relatives at dexmedetomidine 2.0 μg/kg. Children patients who fell asleep were clam without awaking when they were separated from their relatives at dexmedetomidines 2.5 μg/kg and 3.0 μg/kg, indicating a nasal spray with dexmedetomidines 2.5 μg/kg and 3.0 μg/kg can quickly get the children into sleep and has a higher depth of sleep, which is beneficial to quickly transfer the children patients to the operating room and improve the efficiency.

After entering the room at dexmedetomidine 2.0 μg/kg, the children patients awoke again after taking off the face mask, and sevoflurane induction could not be performed quietly. After entering the room at dexmedetomidine 2.5 μg/kg and 3.0 μg/kg, the children patients were still quite after taking off the face mask, and sevoflurane induction could be performed successfully to establish intravenous access, thus dexmedetomidine 2.0 μg/kg is insufficient to maintain satisfactory sedation,

children patients were arousal during anesthesia induction, and there was potential for psychological trauma, while dexmedetomidines 2.5 μg/kg and 3.0 μg/kg provided satisfactory sedation and increased children patients' comfort.

After the end of surgery, the awakening time of the children patients increased with the increase of dexmedetomidine dose, indicating that the duration of sedation is longer with the increase of dexmedetomidine dose, and that the increase of awakening time of propofol and remifentanil, dexmedetomidine and general anesthesia drugs have synergistic effects[12], which may increase the action time due to the combination of several drugs. Therefore, the increase of dexmedetomidine dose and the reduction of the dose of general anesthesia medication may be considered to achieve rapid awakening.

The family members of the children patients were satisfied with dexmedetomidines 2.5 μg/kg and 3.0 μg/kg, it is generally accepted by the family that the children patients entered the operating room without any crying, and the children patients were quiet after awakening with little crying. It is believed that the children patients did not suffer, which is the characteristic of dexmedetomidine. After awakening, the residual dexmedetomidine in the children patients' body may cause the children patients to be sedated, but the stimulation can make children patients awaken without respiratory depression, which makes dexmedetomidine safe for preoperative sedation, reduces the children patients' family's worry to the children patients, and increases the family's satisfaction. However, in the dexmedetomidine nasal spray 3.0 μg/kg group, the awakening time was slightly prolonged, and the children patients' family members believed the waiting time was slightly longer and they were slightly dissatisfied.

Dexmedetomidines at all doses produced no serious complications such as respiratory depression and severe low heart rate, and therefore, all three doses of nasal spray dexmedetomidine were safe for clinical use, and given the waiting time of the patients' family, nasal spray dexmedetomidine 2.5 μg/kg was more suitable clinical sedation before surgery.

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