INFLUENCE OF DEXMEDETOMIDINE ON CLINICAL EFFICACY OF GENERAL ANESTHESIA AND STRESS RESPONSE IN CHILDREN

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Abstract

This study was aimed to explore the effect of dexmedetomidine (DEX) nose drops on paediatric general anaesthesia in the resuscitation room and its influence on children’s postoperative stress. Sixty-eight children undergoing general anaesthesia were enrolled. They were randomly divided into two groups according to admission, with 34 cases in each group. Children in the experimental group received DEX at a 1µg/kg dose as nasal drops, combined with sevoflurane (SEV) anaesthesia. Children in the control group received 0.4 mL saline as nasal drops, combined with SEV anaesthesia. Mean arterial pressure (MAP) and heart rate (HR) were recorded before induction of anaesthesia (T0), during extubation (T1), 5 min (T2), and 15 min after extubation (T3). In addition, venous blood was sampled at each of the above time points to determine the plasma epinephrine (E), norepinephrine (NE), and cortisol (Cor) levels to evaluate the postoperative stress response. The incidence of adverse reactions in the two groups was counted. The rate of crying at T1, restlessness after awakening, and adverse reactions were significantly reduced in children from the experimental group compared with the control group. The induction time of anaesthesia in children in the experimental group was significantly decreased compared with the control group. There was no considerable difference in the awakening time of the two groups of children, and the stay time in the post-anesthesia care unit (PACU) was not extended. In addition, the children in the experimental group had lower MAP and HR at the time of extubation and 5 minutes after extubation compared with the control group. At T1 and T2, the changes of plasma E, NE, and Cor in children from the experimental group were significantly decreased compared with the levels in the control group.

Rezumat

Acest studiu și-a propus să exploreze efectul picăturilor nazale cu dexmedetomidină (DEX) asupra anesteziei generale pediatrică și influența acestuia asupra stresului postoperator al copiilor. În studiu au fost inclusi 68 de copii, randomizați în două grupuri. Copiii din grupul experimental au primit DEX la o doză de 1 µg/kg sub formă de picături nazale, în combinație cu anestezie cu sevoflurane (SEV). Copiii din grupul de control au primit 0,4 mL soluție fiziologică sub formă de picături nazale, combinată cu anestezie SEV. S-au înregistrat valorile tensiunii arteriale medii (MAP) și frecvența cardiacă (HR) înainte de inducerea anesteziei (T0), în timpul extubării (T1), la 5 minute (T2) și la 15 minute după extubare (T3). În plus, s-a recoltat sânge pentru fiecare dintre momentele de mai sus pentru a determina nivelurile plasmatice a epinefrină (E), norepinefrină (NE) și cortisol (Cor), în scopul evaluarii răspunsului la stres postoperator. S-a evaluat, de asemenea, incidența reacțiilor adverse în cele două grupuri. Timpul de inducere a anesteziei la copiii din grupul experimental a fost semnificativ redus comparativ cu grupul de control. Nu a existat o diferență considerabilă în timpul de trezire al celor două grupuri de copii, iar timpul de staționare în unitatea de îngrijire post-anestezie (UCPA) nu a fost prelungit. În plus, copiii din grupul experimental au avut MAP și HR mai scăzute la momentul extubării și la 5 minute după extubare, comparativ cu grupul de control. La T1 și T2, modificările plasmatice a E, NE și Cor la copiii din grupul experimental au fost semnificativ scăzute în comparație cu nivelurile din grupul de control.

Keywords: dexmedetomidine, sevoflurane, inhalation anaesthesia, stress response

Introduction

In the case of infants and young children that underwent surgery very often occurs, preoperative anxiety often occurs [1]. Children can’t cooperate, and surgery is not finalized under local anaesthesia [2]. To effectively alleviate preoperative anxiety in children, the best way is to give appropriate medication before surgery. Traditional intravenous anaesthesia usually uses Ketamine [3]. Children with large secretions in the respiratory tract are prone to respiratory depression, and the recovery time is long, and they are prone to agitation during the recovery period [4]. Clinical experience has shown that Sevoflurane (SEV) can also be adopted as one of the drugs for preoperative anaesthesia in infants and young children. Such drugs are highly volatile and have a unique fruity fragrance. The difficulty of using the medicine is significantly reduced [5, 6]. Compared with other volatile anaesthetics, SEV minimizes the irritation of the upper respiratory tract of children, significantly shortening the time it takes for the drug to take effect.
and wash out [7]. However, before the induction of anaesthesia, the child feared being separated from his family and the operating room environment and often cried. Therefore, giving sedation before inducing anaesthesia in children can help eliminate or reduce the fear. Dexmedetomidine (DEX) is an α2 receptor agonist that acts on the spinal cord and related receptors on the spinal cord. It has sedative, analgesic, and anti-sympathetic effects and does not affect breathing. It is especially suitable for infants and young children to calm and analgesia [8]. The effect of DEX nasal drops combined with SEV inhalation anaesthesia in children's short surgery was explored in this work. Every index of the child was observed, recorded and scored.

**Materials and Methods**

**Study design**

Sixty-eight children aged 1 to 5 years old undergoing general anaesthesia in the anaesthesia resuscitation room in the Mindong Hospital Affiliated with Fujian Medical University from February 2019 to August 2020 were randomly selected and included in the study. They were randomly divided into DEX nasal drip combined with SEV anaesthesia group (experimental group) and only SEV inhalation group (control group), 34 cases per group. Children with congenital cardiovascular disease, respiratory infections, respiratory malformations, neurological diseases, drug allergies, or obesity were excluded. Before the operation, the electrocardiogram (ECG), chest radiograph, blood routine, electrolyte and liver and kidney function tests of the two groups of children were normal. There was no significant difference in general information between the two groups of patients (p > 0.05). The same group of surgeons performed all operations. This work was approved by the Ethical Committee of the Mindong Hospital, affiliated with Fujian Medical University, and the informed consent forms were signed by the patient’s parents or legal representative.

**Inclusion criteria:** the patients who met the criteria for children undergoing general anaesthesia in the recovery room of the anaesthesia room; aged below 5 years old; American Society of Anaesthesiologists (ASA) classification of the child was level I-II; the child’s ECG, chest radiograph, blood routine, electrolyte and liver and kidney function tests were all normal; no abnormality in the growth and development of the child; the child hadn’t received DEX or other α2 receptor agonists or related drugs that affect the results of the experiment one month before the operation; the legal representative of the child signed the informed consent.

**Exclusion criteria:** children with fever, cold, cough, and other diseases; children with asthma and other respiratory diseases; children with epilepsy and other neurological disorders; children that had undergone head surgery or traumatic brain injury; children with known drugs allergy.

**Anaesthesia procedure**

The two groups were routinely fasted for 6 hours before the operation and forbidden to drink liquids for 2 hours. Both groups of children didn’t take any preoperative medication. Children in the experimental group received 1 µg/kg bw DEX (China Jiangsu Hengrui Pharmaceutical Co., Ltd., China) as intranasal drops. The drug should be instilled in the left and right nostrils in equal amounts, and the DEX specification used was 100 µg/mL. Children in the control group received 0.4 mL saline as nasal drops. The children in the two groups were accompanied and monitored by specialized anaesthesiologists and parents before starting the operation after the medication was completed. After waiting for 30 minutes in the waiting area, the two groups of children were anaesthetized by inhalation Sevoflurane (SEV, Shanghai Hengrui Pharmaceutical Co., LTD., China) using the tidal volume method. The breathing circuit of the anaesthesia machine was pre-charged for the 60s, the SEV volatilization tank scale was adjusted to 8%, and the oxygen flow was 8 L/min. A mask was given to inhale SEV while a specific nurse played with the child. When the eyelash reflex disappeared after the child fell asleep, the SEV was adjusted to 5% and the oxygen flow to 2 L/min. After the operation, the SEV volatilization tank was closed, and the oxygen flow was adjusted to 6 L/min. According to the partial pressure of end-tidal carbon dioxide (PetCO2) and respiratory frequency monitoring, autonomic, auxiliary, or controlled respiration was implemented, PetCO2 and respiratory frequency were maintained within the normal range.

**Clinical indicators**

The child’s mean arterial pressure (measured with Blood pressure monitor, Nanjing Beideng Medical Co., LTD., China), heart rate (HR, measured with a Heart rate monitor, Shanghai Sanwei Medical Equipment Co., LTD., China), electrocardiogram (ECG, measured with Electrocardiogram machine, China Jinan Ailaibao Instrument Equipment Co., LTD., China), and pulse oxygen saturation (SPO2, measured with Oxygen saturation measuring instrument, China Shanghai Sanwei Medical Equipment Co., LTD., China) were continuously monitored.

The crying situation of the two groups of children was recorded before or during induction, induction time (from administration to disappearance of eyelash reflex). The other monitored parameters were: the operation time (from the start of surgical disinfection to the end of the operation), wake up time (from the end of the operation to the time the child recovered from consciousness), and restlessness after waking. After the procedure, the laryngeal mask was removed under deep anaesthesia, oral secretions were aspirated, and the patient was transferred to the post anaesthesia care unit (PACU) for observation. Mean arterial pressure (MAP) and heart rate (HR) were recorded before induction of anaesthesia (T0),
periorative hemodynamic changes between the two groups

Table III

| Indicator | Group          | T0        | T1        | T2        | T3        |
|-----------|----------------|-----------|-----------|-----------|-----------|
| MAP (mmHg)| Experimental group | $75.25 \pm 6.31$ | $90.27 \pm 7.21^*$ | $84.16 \pm 5.53^*$ | $78.27 \pm 6.05$ |
|           | Control group   | $76.08 \pm 5.58$ | $103.26 \pm 8.05^*$ | $91.08 \pm 5.31^*$ | $81.31 \pm 6.27$ |
| HR (min)  | Experimental group | $102.14 \pm 5.91$ | $117.10 \pm 6.33^*$ | $107.17 \pm 5.27^*$ | $101.86 \pm 3.96$ |
|           | Control group   | $101.26 \pm 4.88$ | $133.95 \pm 6.17^*$ | $120.25 \pm 5.43^*$ | $107.90 \pm 5.28$ |

*p < 0.05 compared with T0; *p < 0.05 compared with the control group. MAP: mean arterial pressure; HR: heart rate

Results and Discussion

General information of the patients

No significant difference in gender, age, weight, operation time, and PACU stay time between the two groups of children (p > 0.05) were observed at the beginning of the study (Table II).

Statistical analysis

SPSS19.0 statistical software (IBM, USA) was used for data analysis. Measurement data were expressed as mean ± standard deviation and paired t-test was adopted to compare groups. A Chi-square test was employed for counting data. p < 0.05 indicated that the difference was statistically significant.
Changes in plasma epinephrine, norepinephrine, and cortisol levels
At T1 and T2, plasma E, NE, and Cor levels increased in both groups compared with T0 levels (p < 0.05). At T1 and T2, the control group's E, NE and Cor levels were significantly increased compared with the experimental group (p < 0.05). At T3, no significant difference has been observed in E, NE and Cor levels between the two groups (Table IV).

| Indicator | Group     | T0             | T1             | T2             | T3             |
|-----------|-----------|----------------|----------------|----------------|----------------|
| E (nmol/L)| Experimental group | 36.36 ± 12.17 | 66.54 ± 11.42*# | 49.75 ± 12.08*# | 37.26 ± 10.16  |
|           | Control group | 37.17 ± 11.27  | 108.61 ± 13.48* | 93.74 ± 14.63* | 40.16 ± 13.84  |
| NE (nmol/L)| Experimental group | 98.20 ± 21.33 | 175.41 ± 28.08** | 154.29 ± 23.16** | 110.47 ± 22.68 |
|           | Control group | 96.37 ± 20.78  | 203.36 ± 31.24* | 179.16 ± 24.27* | 121.51 ± 25.88 |
| Cor (µmol/L)| Experimental group | 401.76 ± 75.67 | 708.79 ± 83.64** | 584.06 ± 87.37** | 451.75 ± 83.46 |
|           | Control group | 404.09 ± 79.43 | 817.15 ± 90.17* | 689.17 ± 86.75* | 510.33 ± 85.57* |

Note: *p < 0.05 compared with T0; p < 0.05 compared with the control group

Comparison of crying during induction, induction time, wake-up time, pain score and restlessness score
In the control group, 21 cases (61.76%) cried during induction compared with only 7 patients (20.59%) in the experimental group. Compared with the control group, crying was significantly reduced in the experimental group (p < 0.05). The experimental group's induction time, postoperative pain score, and pain score were significantly inferior to those of the control group (p < 0.05). There was no substantial difference in the wake-up time between the two groups of children (p > 0.05) (Table V).

| Group       | Indication | Crying during induction (n [%]) | Induction time (s) | Wake-up time (min) | Pain scores | Restlessness scores (points) |
|-------------|------------|--------------------------------|-------------------|-------------------|-------------|-------------------------------|
| Control group | 21 (61.76) | 52.54 ± 5.13                  | 9.56 ± 1.45       | 6.15 ± 1.12       | 2.50 ± 1.50 |
| Experimental group | 7 (20.59)* | 40.87 ± 5.97*                 | 9.21 ± 1.32       | 3.08 ± 1.35*      | 1.50 ± 0.50* |

*p < 0.05 compared with the control group

Adverse reactions
None of the children in the experimental group had adverse reactions such as respiratory depression, vomiting, laryngospasm and bradycardia. Only a few children developed agitation. The adverse reaction rate was notably lower than that of the control group (p < 0.05) (Table VI).

| Group       | Respiratory depression (n) | Vomiting (n) | Laryngospasm (n) | Bradycardia (n) | Restlessness (n) | Incidence (%) |
|-------------|----------------------------|--------------|------------------|-----------------|-----------------|---------------|
| Experimental group | 0                     | 0            | 0                | 0               | 2               | 5.88*         |
| Control group     | 2                      | 1            | 1                | 1               | 6               | 32.35         |

*p < 0.05 compared with the control group

DEX can be administered via the intravenous or nasal mucosal routes [11]. Due to the low irritation to the mucous membrane, the bioavailability of absorption through the nasal mucosa reaches 65% ~ 80%. Therefore, for children without intravenous access, DEX nasal drops is also a very effective route of administration [12]. DEX of 1, 2 and 3 µg/kg instilled through the nose can produce suitable sedation. Therefore, the 1 µg/kg concentration in the nose was selected for this study.

In this work, DEX nasal drops combined with mask inhalation of SEV anaesthesia was used for children's short surgery. The results showed that compared with the simple SEV mask inhalation anaesthesia group, the DEX nasal drop combined SEV mask inhalation group had lower MAP and HR 5 minutes after extubation. It was suggested that DEX nasal drops could reduce sympathetic nerve excitation during the extubation period of children and had a good sedative effect. Compared with the control group, the rate of crying during induction in the experimental group was significantly reduced. In addition, the proportion of restlessness after waking up was also significantly reduced. The induction time of anaesthesia in children in the experimental group was notably shorter than in the control group. There was no noticeable difference in the awakening time between the two groups of children, and the stay time in the PACU was not extended. It was suggested that DEX nasal drops had no effect on the recovery time of children, and it was safe and effective.
Extubation of the trachea is a severe body stimulus, which will cause a series of stress responses in the body, such as increased blood pressure and increased heart rate [13, 14]. It may be related to various factors such as shallow anaesthesia during tracheal extubation, mechanical irritation of the tracheal tube, wound pain and sputum suction operation [15, 16]. It can cause many complications during extubation, such as laryngospasm, vomiting and aspiration of stomach contents [17]. DEX is a new, specific and highly selective α2 receptor agonist. It can inhibit the release of norepinephrine and produce sedation, having anti-anxiety and analgesic effects, mainly in the locus coeruleus, with no effect on the respiratory centre and no respiratory inhibition [18, 19]. In this work, DEX nasal drops combined with SEV anaesthesia was evaluated. At the time of extubation and 5 minutes after extubation, the plasma E, NE and Cor changes were significantly lower than those of the control group. It was related to the pharmacological effects of DEX. First, DEX has anti-anxiety, analgesic and sedative effects, enhancing the body’s tolerance to adverse stimuli and better inhibiting the stress response during tracheal extubation [20]. Second, DEX has a central anti-sympathetic effect, antagonizing the increase in blood pressure, mainly sympathetic excitement during extubation, increased heart rate and increased myocardial oxygen consumption, making haemodynamics more stable [21]. DEX attenuates various stimuli, such as stress response after extubation, and improves cardiovascular stability. It is safe, effective and easily tolerated.

Conclusions
This study supports that DEX nasal drops combined with mask SEV inhalation produce fast anaesthesia in children. Children woke up quickly, and anaesthetize was smooth, which inhibited the stress response of children with tracheal extubation after general anaesthesia, and didn’t affect the recovery time after surgery. Further studies on higher cohorts should validate these findings.

Conflict of interest
The authors declare no conflict of interest.

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