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**The Safety、Efficacy and Pharmacokinetics of  
Dexmedetomidine Administered Through Different Routes  
in Pediatric**

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# **The safety、efficacy and pharmacokinetics of dexmedetomidine administered through different routes in pediatric**

Dexmedetomidine (DEX) is a highly selective  $\alpha_2$  adrenoreceptor agonist that provides anxiolysis, sedation, and modest analgesia with minimal respiratory depression. DEX is approved for use in adults; however, there continues to be no U.S. Food and Drug Administration (FDA)-approved label indication for DEX in pediatric patients. Nevertheless, DEX has been reportedly used in pediatrics as a premedication, a sedation agent for use in the pediatric intensive care unit, an adjunct to inhaled anesthetic agents, and a drug for both the prophylaxis and the treatment of emergence agitation (EA) after general anesthesia. EA, especially in pediatrics, poses a significant challenge to quality patient care. Although 2-, 5-, or 10-minute DEX infusions reduce the incidence of EA in children, a rapid bolus injection, if proven to be hemodynamically acceptable, would allow a more timely and optimum administration of the drug to both treat and prevent EA. Jooste et al had observed that rapid IV bolus administration of dexmedetomidine in 12 children having undergone heart transplants was clinically well tolerated, although it resulted in a transient but significant increase in systemic and pulmonary pressure and a decrease in HR. John A et al also reported that rapid IV bolus administration of 0.5 $\mu$ g/kg DEX in children improved their recovery profile by reducing the incidence of EA. Although a statistically significant change in hemodynamics was observed, but no patients required any intervention for hemodynamic changes. But either a small sample study, or only one dose of DEX. Dexmedetomidine is used frequently to prevent and treat postoperative agitation in doses of 0.25–1 $\mu$ g/kg, and it is now common practice in clinical institution to administer dexmedetomidine as a rapid (less than 5 seconds) IV bolus. We therefore designed the research to study the efficacy, safety and pharmacokinetics of different doses of dexmedetomidine as a rapid bolus for pediatric patients.

On the other hand, our previous study revealed that intranasal dexmedetomidine premedication can low the preoperative anxiety and postoperative EA in pediatric. The nasal delivery is non-invasive, comfortable and easy to accept by children. So our further research is to study the pharmacokinetics after a single dose of dexmedetomidine administered as a nasal spray in pediatric.

## **1.Acute hemodynamic and respiratory changes after rapid intravenous different doses of dexmedetomidine in Pediatric**

### **1. 1 Patients' selection**

Inclusion: (1) selective operation of inguinal hernia repair in children; (2) aged 3-9 years; (3) ASA I - II; (4) enter the operating room by himself without parents; (5) normal liver and kidney function; (6) no history of anesthesia medication allergy.

Exclusion criteria: (1) allergic to dexmedetomidine, similar active ingredients or excipients; (2) G-6-PD deficiency; (3) a history of arrhythmia, bronchial and

cardiovascular diseases, abnormal liver function and so on; (4) a history of use of alpha 2 receptor agonists or antagonists.

After obtained informed written consent from all parents, 100 pediatric patients were randomly enrolled into five groups: group 1.1: control group; group1.2: 0.25 $\mu$ g/kg dexmedetomidine group; group1.3: 0.5 $\mu$ g/kg dexmedetomidine group; group1.4: 0.75 $\mu$ g/kg dexmedetomidine group; group1.5: 1 $\mu$ g/kg dexmedetomidine group.

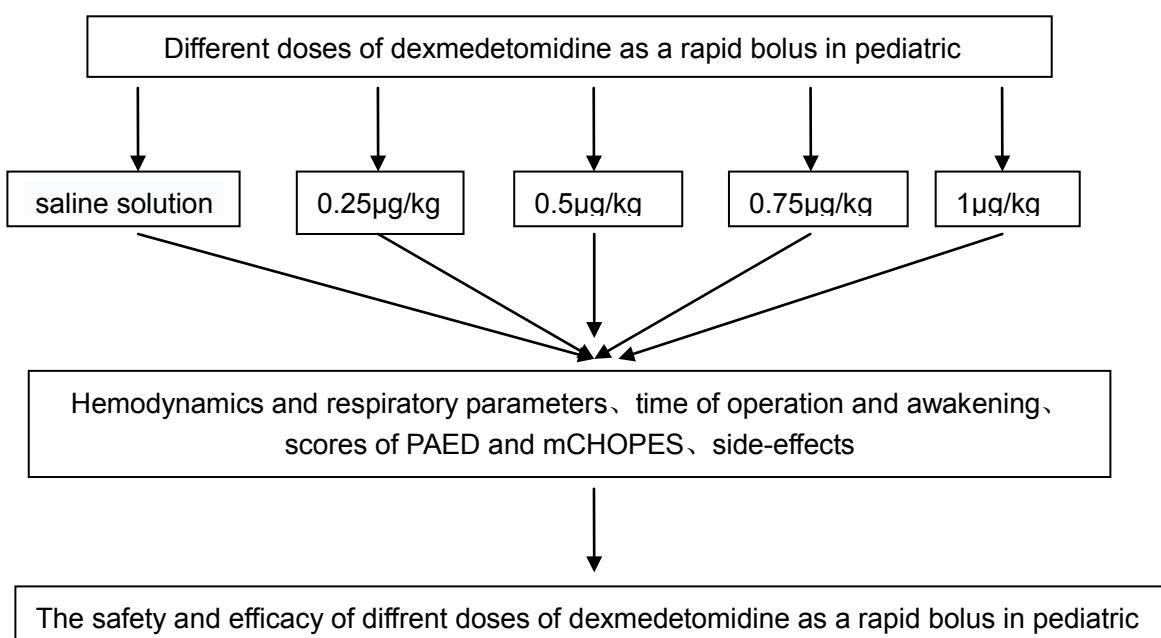
## 1.2 Medication

There was no premedication used. A peripheral venous catheter was placed about 2 h before operation on the ward. EMLA cream (lidocaine 2.5 % and prilocaine 2.5 %, Astra Zeneca Inc., Sweden) was applied to facilitate the venous cannulation. Heart rate, noninvasive arterial blood pressure, peripheral arteriolar oxygen saturation, ECG and BIS were monitored. After preoxygenation via face mask, anesthesia was induced with propofol 2–3 mg/kg and inhalation of 6 vol% sevoflurane. After pupil is fixed, put into the LMA and do the Ilioinguinal/iliohypogastric nerve block (IINB) to relieve postoperative pain. Anesthesia maintained with 2–3 vol% sevoflurane and spontaneous respiration. After the vital signs are stable, study groups receive a rapid bolus injection of different dose of DEX at a rate of less than 5 seconds, whereas patients in control group received saline in an equal volume.

## 1.3 Data collection

HR, SBP, DBP, RR, VT, SaO<sub>2</sub> and BIS will be recorded immediately before the study drug injection (baseline) and every minute for 5 minutes thereafter. EA was assessed by the study staff upon arrival in the PACU using the Pediatric Anesthesia Emergence Delirium (PAED) scale (0–20 scale) and pain score using the mCHOPES scale. The time of operation and awakening, and any side-effects such as respiratory/cardiovascular depression should be recorded.

## 1.4 Technical route



## 2. Pharmacokinetics after a single rapid intravenous dose of dexmedetomidine in Pediatric

### 2.1 Patients' selection

selective operation of orthopedics operation or general surgery operation in children, others are the same as 1.1. 48 pediatric patients were randomly enrolled into four groups: group2.1: 0.25 $\mu$ g/kg dexmedetomidine group; group2.2: 0.5 $\mu$ g/kg dexmedetomidine group; group2.3: 0.75 $\mu$ g/kg dexmedetomidine group; group2.4: 1 $\mu$ g/kg dexmedetomidine group.

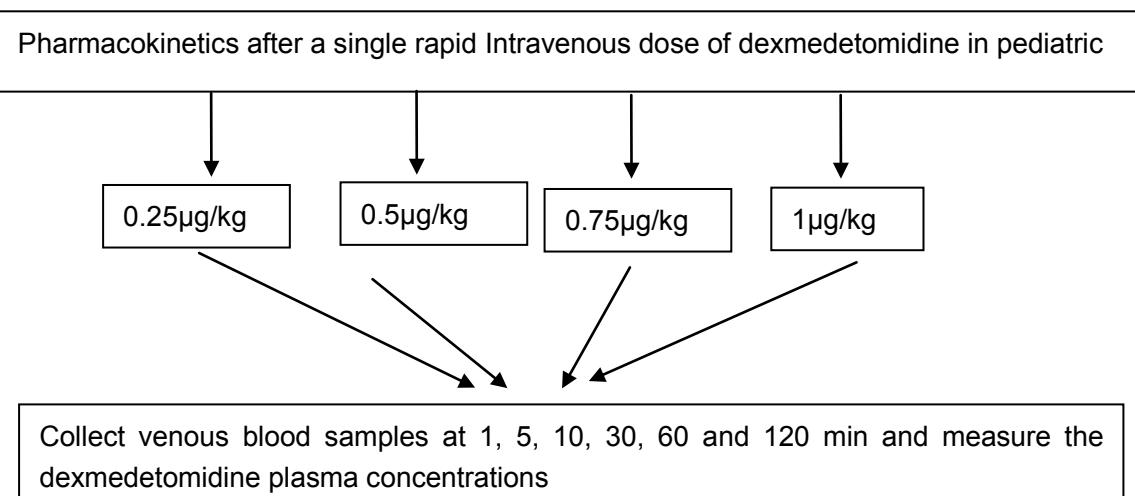
### 2.2 Medication

There was no premedication used. A peripheral venous catheter was placed about 2 h before operation on the ward. EMLA cream (lidocaine 2.5 % and prilocaine 2.5 %, Astra Zeneca Inc., Sweden) was applied to facilitate the venous cannulation. Heart rate, noninvasive arterial blood pressure, peripheral arteriolar oxygen saturation, ECG and BIS were monitored. After preoxygenation via face mask, anesthesia was induced with propofol 2–3 mg/kg and inhalation of 6 vol% sevoflurane. After pupil is fixed, put into the LMA and different regional nerve block or catheter was carried out to relieve postoperative pain. Anesthesia maintained with 2–3 vol% sevoflurane. After the vital signs are stable, study groups receive a rapid bolus injection of different dose of DEX at a rate of less than 5 seconds.

### 2.3 Blood sampling

Venous blood samples of 0.4 ml each were collected at the following times: 1, 5, 10, 30, 60 and 120 min after the end of the infusion of dexmedetomidine. Blood samples were drawn into EDTA tubes and stored at 4 °C. All heparinized blood samples were centrifuged within 30 min after collection, and the supernatant plasma was pipetted into glass vials and stored at -30 °C immediately after separation. Later on, the samples were stored at -80 °C until analysis. Dexmedetomidine plasma concentrations were measured with high-performance liquid chromatography and mass spectrometry.

### 2.4 Technical route



### **3. Pharmacokinetics after a single dose of dexmedetomidine administered as a nasal spray in pediatric**

#### **3.1 Patients' selection**

The same as 2.1,39 pediatric patients were randomly enrolled into three groups: group3.1: 1.0  $\mu\text{g}/\text{kg}$  dexmedetomidine group; group3.2: 1.5  $\mu\text{g}/\text{kg}$  dexmedetomidine group; group3.3: 2.0  $\mu\text{g}/\text{kg}$  dexmedetomidine group.

#### **3.2 Medication**

There was no premedication used. A peripheral venous catheter was placed about 2 h before operation on the ward. EMLA cream (lidocaine 2.5 % and prilocaine 2.5 %, Astra Zeneca Inc., Sweden) was applied to facilitate the venous cannulation. Heart rate, noninvasive arterial blood pressure, peripheral arteriolar oxygen saturation, ECG and BIS were monitored. After preoxygenation via face mask, anesthesia was induced with propofol 2–3 mg/kg and inhalation of 6 vol% sevoflurane. After pupil is fixed, put into the LMA and different regional nerve block or catheter was carried out to relieve postoperative pain. Anesthesia maintained with 2–3 vol% sevoflurane. After the vital signs are stable, study groups receive intranasal different dose of DEX.

#### **3.3 Blood sampling**

Venous blood samples of 0.4 ml each were collected at the following times: 10, 30, 60, 120, 180 and 240 min after the end of administration of dexmedetomidine. Blood samples were drawn into EDTA tubes and stored at 4 °C. All heparinized blood samples were centrifuged within 30 min after collection, and the supernatant plasma was pipetted into glass vials and stored at -30 °C immediately after separation. Later on, the samples were stored at -80 °C until analysis. Dexmedetomidine plasma concentrations were measured with high-performance liquid chromatography and mass spectrometry.

#### **3.4 Technical route**

