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The effect of premedication with budesonide aerosol inhalation on the incidence of respiratory adverse events during anesthesia recovery period in pediatric patients.

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Abstract

Objective: We aimed to investigate the influence of premedication with budesonide aerosol inhalation on the incidence of respiratory adverse events during anesthesia recovery period in pediatric patients.
Method: 120 pediatric patients underwent elective surgery of inguinal hernia repair were enrolled in the study. They were given two different types of anesthesia, group A received general anesthesia with the Laryngeal Mask (LMA), and group B were treated with budesonide aerosol inhalation preoperatively before general anesthesia with LMA. The incidence of adverse events which included laryngospasm, respiratory tract infection, the length of Post-Anesthesia Care Unit (PACU) staying, the volume of throat secretions and hoarseness were monitored closely.
Results: Compared with group A, group B had a lower incidence of respiratory adverse events.
Conclusion: Preoperative budesonide aerosol inhalation could reduce the incidence of respiratory adverse events during the anesthesia recovery period in children.

Keywords: Budesonide, Aerosol inhalation, Anesthesia, Pediatric, Respiratory adverse events.

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Introduction

In pediatric surgery, general anesthesia is applied for almost all the cases. Pediatric patients, especially infants have their own characteristics in anatomy, physiology and pharmacology in comparison with adults [1]. Coupled with the physiological changes caused by disease, pediatric surgery brought a severe challenge to clinical anesthesia. Respiratory Adverse Events (RAEs) were very common in pediatric patients during perioperative period [2]. In cardiac procedures under anesthesia, the incidence of RAEs was up to 45 % [3]. The risk of RAEs decreased by 8 % in every increased year of age, and children not being cared for by a specialized pediatric anesthesiologist had a 1.7-fold increased risk for RAEs [4]. With the rapid development of new monitoring devices and pharmacological products, the perioperative mortality and the occurrence of critical incidents reduced significantly [5]. However, perioperative RAEs were still very common and were the major causes of claims reported in pediatric patients. Due to the potential impact of RAEs, more attention should be paid in clinic.

Pharyngalgia, cough, hoarseness and laryngospasm were the main postoperative throat complications after anesthesia. Previous studies suggested that laryngospasm was always occurred due to the increase of respiratory secretions, the mechanical irritations of endotracheal tube and the effects of anesthetic drugs, as well as the upper respiratory tract infections/potential infection and the suppression of mucociliary clearance by dry airflow during ventilation [6-8]. The occurrence of laryngospasm could bring rapid deterioration in systemic oxygenation and cyanosis, and decrease in surplus pulse O_2 (SpO_2), even become life-threatening if some interventions were delayed [8,9]. As reported, the prevalence of laryngospasm in children younger than 6 years old was 14 % [10] and children older than 6 y old were 3.6 % [11].

The establishment of artificial airway was essential to reduce the incidence of postoperative throat complications during the process of anesthesia. The commonly used methods for artificial airway were endotracheal tube, Laryngeal Mask (LMA) and facemask. As reported, the incidence of RAEs for LMA was lower than endotracheal tube [12]. Corticosteroids were widely used to prevent and alleviate postoperative throat complications. Budesonide was an anti-inflammatory corticosteroid approved by Food and Drug Administration (FDA), and it was the first and only inhaled corticosteroid that

could be delivered by atomization inhalation. Budesonide had a stronger lipophilicity and was beneficial to play a local anti-inflammatory activity when compared with other systemic corticosteroids. Budesonide can be delivered to the airway without introducing a systemic exposure after released into human body. It can enhance the vascular tension of throat and reduce the capillary permeability, and it also can inhibit the formation of edema and inflammatory reactions of the local tissue [13,14].

This study evaluated the incidence of RAEs in pediatric patients who received the elective surgery of inguinal hernia repair. We aimed to investigate the influence of budesonide aerosol inhalation for pediatric anesthesia on the incidence of RAEs.

Materials and Method

Patients

From December 2012 to February 2014, children who underwent elective surgery of inguinal hernia repair in Sichuan Provincial People's Hospital were enrolled in the study. The inclusive criteria were listed as follows: (i) Aged in 1-3 y old and weighed 6-17 kg; (ii) The American Society of Anesthesiologists (ASA) graded I-II; (iii) Without difficulty in cannula before surgery; (iv) Without serious systemic diseases; (v) Without respiratory infections. The children received two different types of anesthesia. Children in group A used LMA for general anesthesia, and children in group B were treated with budesonide aerosol inhalation (1 mg) preoperatively before general anesthesia with LMA. All the patients had normal indexes in preoperative examinations. The operation time was less than 1 h, and the bleeding volume was less than 5 ml. The anesthesia induction and maintenance for all the operations were successful. The hypoxia, low blood pressure or decreased heart rate was not occurred during the whole process. Children with one of the following conditions were excluded: (i) the children who cried severely and had excessive secretions when entering operation room; (ii) the children who cooperated poorly, and had the bad effect of aerosol inhalation; (iii) the children whose induction and maintenance procedures of anesthesia were contrary to the pre-plans (as follows) due to individual differences or operation conditions; (iv) the time consumed from induction of anesthesia to the end time was longer than 1 h; (v) the children whose recovery process during the anesthesia recovery period was not in conformity with that described in the protocol. The study was approved by the Institutional Ethics Committee of Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital. Written informed consents were obtained from all patients' parents before being enrolled into the study.

Anesthesia

The patients were visited at the day before operation, and in order to improve the children's therapeutic compliance degree during the operation, the children were given the child's masks to be familiar with them. The patients in group B were treated with 1 mg budesonide (Corden Pharma SpA Caponago, Italy) *via* aerosol inhalation before anesthesia. Both groups A and B adopted sevoflurane (Maruishi Pharmaceutical Co., Ltd., Osaka, Japan) for inhalational induction of anesthesia, then the courses of fluid infusion were established when children fall asleep. The Heart Rate (HR), Electrocardiograph (ECG), saturation of pulse oximetry (SpO_2) and blood pressure were monitored continuously. All the patients were induced by intravenous injection with atropine (0.01-0.02 $mg•kg^{-1}$; Runhong, Xinzhen, China), midazolam (0.08-0.10 $mg•kg^{-1}$; Enhua Co., Xuzhou, China), propofol (1-2 $mg•kg^{-1}$; Fresenius Kabi Australia GmbH, Sydney), cisatracurium besilate (0.10-0.15 $mg•kg^{-1}$; Dongying, Nantong, China) and fentanyl (2-4 $\mu g•kg^{-1}$; Renfu, Yichang, China) successively. LMA was placed at the appropriate depth of anesthesia.

Air-oxygen mixture with 60% oxygen and 2-3% sevoflurane were inhaled, coupled with 0.1 $\mu g•kg^{-1}•min^{-1}$ remifentanil were used for the maintenance of anesthesia after operation. The administrations of anesthetic drugs were stopped after the end of skin suture, and 1 ml 0.25 % ropivacaine was used for the local anesthesia to ease the pain of skin incisions. Oxygen at a flow rate of 6 $L•min^{-1}$ was used for pre-oxygenation to wash the lungs. When the children's respiratory rate reached to 20-25 bpm, tidal volume reached to 6-8 $ml•kg^{-1}$ and the concentration of exhaled sevoflurane was under 0.5%, they were transferred to the PACU. The extubation was conducted under the following conditions: respiratory rate reached to 20-25 bpm, tidal volume reached to 8-10 $ml•kg^{-1}$, the protective reflexes such as swallowing and coughing were recovered, HR and non-invasive Blood Pressure (NiBP) remained stable, SpO_2 was greater than 98%, and the children regained consciousness without external stimulus. Assisted mask ventilation was applied if SpO_2 declined or laryngospasm occurred after removing LMA. The anesthesiologist judged the necessity of reintubation and drugs, and they made records. The patients transferred from PACU to wards when they were fully awake, breathed normally, SpO_2 reached to 95% without oxygen support, enable coughed and expectorated on their own, and NiBP and HR fluctuated within 20% of the preoperative baseline. All anesthesia was judged and carried out by the same anesthesiologist.

Observational content

The postoperative adverse events were observed and collected as follows: (i) The number of cases and the patients' severity of laryngospasm during the intraoperative and postoperative period; (ii) The time stayed in PACU; (iii) The total volume of respiratory secretions during anesthesia recovery period using the suction catheters; (iv) The incidence of postoperative hoarseness, tone changing, and other complications; (v) The incidence of postoperative respiratory infections.

The classification of laryngospasm was defined with the following criteria [15]. Mild laryngospasm; there were glottic stenosis and only true vocal cords showed a contracture, and a shrill and high-pitched laryngeal stridor occurred when aspirating. Moderate laryngospasm: both the true and false

vocal cords showed contractures, and the resistance of expiration was increased and a rough/low laryngeal stridor was appeared. Severe laryngospasm: the glottis was closed completely, and the intercostal and diaphragm subsided and the ventilation is interrupted.

Statistical analysis

SPSS 19.0 software was used for statistical analysis. Measurement data were expressed as mean ± Standard Deviation (SD) and assessed by t-test. Continuous data were assessed by Chi-square test. Ranked data were analysed by Rank-Sum test. P value less than 0.05 is indicated as statistically significant differences.

Results

General information

There were 120 pediatric patients, and 60 children in each group. Their characteristics were showed in Table 1. There were no significant differences in age, gender, weight and ASA class score between the two groups.

Occurrence and severity of intraoperative and postoperative laryngospasm

Fourteen patients (23.3%) in group A had laryngospasm. Among them, patients with moderate laryngospasm (57.1%) occupied the highest proportion, 5 (35.7%) patients with mild laryngospasm, and 1 (7.1%) patients with server laryngospasm. In group B, only 3 patients had mild laryngospasm. The incidence and severity of laryngospasm in group A was significant higher than that in group B ($P<0.05$) (Table 2).

The length of PACU staying and the total volume of respiratory secretions during the anesthesia recovery period

The average time stayed in PACU was 61.0 ±1 3.3 and 37.0 ± 7.4 min for groups A and B, respectively. The volume of respiratory secretions was 5.0 ± 2.3 and 2.0 ± 0.4 ml, respectively. Compared with group B, the time stayed in PACU was significant longer and more total volume of sputum was observed in group A. The difference was statistically significant ($P<0.05$) (Table 2).

The incidence of complications and postoperative respiratory infections

There were 43 (71.7%) and 11 (18.3%) cases in groups A and B for hoarseness and tone changing, respectively. The rate of complications in group A was significant higher than that in group B ($P<0.05$). The incidence of postoperative respiratory infections was 8 (13.3%) and 1 (1.7%) in groups A and B, respectively. Compared with group A, group B had a significant lower rate of postoperative respiratory infections. There were 23 (39.3%) patients in group A and 11 (18.3%) patients in group B for $SpO_2<95\%$ ($P<0.05$). For recurrent post-operative cough, 13 (26.7%) patients were in group A and 4 (6.7%) patients were in group B ($P<0.05$).

Discussion

There was a high incidence of perioperative critical events in pediatric patients, and more than two-thirds of perioperative critical events were related to the respiratory system [16]. Respiratory problems were very common for children. Children have narrow airway, fragile mucosa and rich vascularity. Therefore, they were susceptible to be infected, and their congestion and swelling in the throat was induced subsequently. The common RAEs included bronchospasm, laryngospasm, respiratory tract infection, hoarseness and tone changing. And the most frequent RAEs would be the laryngospasm. Previous studies found that the ones with laryngospasm had a higher overall number of postoperative complications [17].

Corticosteroids aerosol inhalation could enhance the tension of laryngeal vessels, relieve congestion, and reduce the capillary permeability. It also could mitigate inflammatory exudation and edema in laryngeal mucosa. Therefore, it played a relaxant effect on airway smooth muscle. Budesonide is the only corticosteroid proved by FDA that can be used for aerosol inhalation. It has stronger lipophilicity than other systemic corticosteroids, which is beneficial for its local anti-inflammatory activity [18]. In this study, budesonide was used to reduce RAEs for pediatric patients in anesthesia recovery period.

In the present study, group B with the use of budesonide had a significant lower incidence and severity of laryngospasm in comparison with group A. It demonstrated that budesonide could reduce the occurrence of laryngospasm by relieving laryngeal edema, inhibiting inflammatory response, relaxing the airway smooth muscle and decreasing the glandular secretions. Only 3 cases suffered mild laryngospasm in group B. The reason may be that mucosal edema and infections played important roles in laryngospasm. Preoperative budesonide aerosol inhalation could not reduce the occurrence of laryngospasm completely.

Budesonide was a non-halogenated glucocorticoid with powerful anti-inflammatory effects and high local activity. It reduced the incidence of postoperative laryngospasm, but also positively affected their stay length in PACU, respiratory secretions and the incidence of postoperative respiratory infections. The patients in group B had a lower length of stay in PACU, less respiratory secretions and lower incidence of lung infections than group A. It suggested that the anti-inflammatory effect of budesonide could shorten the anesthesia recovery time and alleviates postoperative anesthesia-related complications.

Laryngeal edema caused by intubation was the main reason for post-anesthetic hoarseness [19]. Budesonide has unique esterification effect, and it can be activated for a long time in the airway to inhibit the tissue edema. Meanwhile, it also could maintain the stability of endothelial cells and reduce the tissue

edema [20]. In this study, the incidence of hoarseness in group B was significantly lower than that in group A. It suggested that budesonide could decrease incidence of postoperative hoarseness remarkably.

As reported, RAEs were more common after general anesthesia [21]. In order to reduce and avoid the adverse effect, many studies focused on the risk factors of RAEs. The results eliminated all the factors related to patients themselves, such as the age of the children, active upper respiratory tract infection, status of the present illness, and morphologic and developmental characteristics [4,22]. Other factors regarding anesthetic management were also significant. Effective guidelines to improve anesthetic practice and management were essential to reduce the incidence of RAEs.

In this study, preoperative application of budesonide aerosol inhalation could remarkably reduce the severity and incidence of postoperative laryngospasm, respiratory infections and postoperative hoarseness and tone changing. Budesonide was suitable for anesthesia in pediatric patients.

Table 1. *The characteristics of preoperative patients.*

	Group A (n=60)	Group B (n=60)
Age (y)	1.8 ± 0.9	2.2 ± 1.0
Gender (male: female)	58:02:00	56:04:00
Weight (kg)	11.5 ± 2.2	13.0 ± 2.2
ASA class (I: II)	57:03:00	58:02:00
Note: ASA: American Society of Anesthesiologists.		

Table 2. *Details of respiratory adverse events. Note: PACU: Post-Anesthesia Care Unit. SpO_2: Surplus pulse O_2. Compared with group B, $^*P<0.05$.*

	Group A (n=60)	Group B (n=60)
Laryngospasm	14 (23.3%)*	3 (5.0%)
Mild	5 (35.7%)	3 (100.0%)
Moderate	8 (57.1%)	-
Severe	1 (7.1%)	-
PACU	61.0 ± 13.3*	37.0 ± 7.4
Hoarseness and tone changing	43 (71.7%)*	11 (18.3%)
Respiratory infections	8 (13.3%)*	1 (1.7%)
SpO_2<95%	23 (39.3%)*	11 (18.3%)
Respiratory secretions (ml)	5.0 ± 2.3*	2.0 ± 0.4
Recurrent post-operative cough	13 (26.7%)*	4 (6.7%)
Glossocoma	37 (61.7%)	46 (76.7%)

Conflict of Interest

All authors declared no conflict of interest.

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