Effect of combined sevoflurane–propofol–fentanyl anesthesia on the postoperative emergence agitation and neuroendocrine compensation in children with tonsillectomy

Chun-Gui Liu, Sheng-Han Zhou, Shou-Bo Quan, Nian-Hua Deng, Qi-Rong Zou

Anesthesiology Department, Dongguan Third People’s Hospital of Guangdong Province, Dongguan 523000, China

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Objective: To study the effect of combined sevoflurane-propofol-fentanyl anesthesia on the postoperative emergence agitation and neuroendocrine compensation in children with tonsillectomy.

Methods: 78 patients who accepted tonsillectomy in our hospital between May 2013 and January 2016 were selected and randomly divided into two groups, the observation group received sevoflurane-propofol-fentanyl anesthesia, and the control group received ketamine-propofol-fentanyl anesthesia, 39 in each group. Before anesthesia, before extubation and at recovery period after extubation, serum was collected respectively to determine the levels of inflammatory factors, stress hormones and renin-angiotensin-aldosterone system (RAAS) system hormones.

Results: Before anesthesia and before extubation, the differences in serum C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, IL-10, cortisol (Cor), norepinephrine (NE), epinephrine (E), free triiodothyronine (FT3), free thyroxine (FT4), renin (PRA), angiotensin II (AT-II) and aldosterone (ALD) levels were not statistically significant between two groups of patients (P>0.05); at recovery period, serum CRP, TNF-α, IL-1β, IL-6, IL-10, Cor, NE, E, FT3, FT4, PRA, AT-II and ALD levels of both groups were significantly higher than those before anesthesia and before extubation (P<0.05), and serum CRP, TNF-α, IL-1β, IL-6, IL-10, Cor, NE, E, FT3, FT4, PRA, AT-II and ALD levels of observation group at recovery period were significantly lower than those of control group (P<0.05).

Conclusion: Combined sevoflurane-propofol-fentanyl anesthesia for children with tonsillectomy can alleviate the inflammatory response and stress response caused by emergence agitation.

1. Introduction

Pediatric tonsillectomy is common surgical procedure of pediatrics. On the one hand, the operation will directly stimulate the throat and cause a variety of adverse reactions, and in order to ensure the smooth progress of operation, it requires enough depth of anesthesia so as to reduce the degree of adverse reaction caused by operation; on the other hand, tonsillectomy can lead to different degree of oropharyngeal cavity mucosa injury and edema, the extubation cannot be done until all sorts of oropharyngeal reactions are fully recovered after surgery, and in order to ensure smooth postoperative extubation, the general anesthetics with short half-life and rapid metabolism are needed[1,2]. Propofol, fentanyl and so on are the common general anesthetics for pediatric tonsillectomy, but because of their short half-life and rapid metabolism, drug withdrawal can cause hyperalgesia and lead to emergence agitation. Emergence agitation will affect the hemodynamic stability, and severe cases may endanger the safety of life[3,4]. Sevoflurane is a new inhalational anesthetic developed in recent years, and it has the advantages of quick induction and recovery as well as strong controllability. In the following study, the effect of combined sevoflurane-propofol-fentanyl anesthesia on the postoperative emergence agitation and neuroendocrine compensation in children with tonsillectomy was analyzed.

Corresponding author: Shou-Bo Quan, Anesthesiology Department, Dongguan Third People’s Hospital of Guangdong Province, Dongguan 523000, China.
Tel: 13580913158
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2. Materials and methods

2.1. Clinical information

78 children who accepted tonsillectomy in our hospital between May 2013 and January 2016 were included, and children’s families signed the informed consent. According to the random number table, the included patients were divided into observation group and control group, 39 cases in each group. Control group received ketamine-propofol-fentanyl anesthesia, there were 20 male cases and 19 female cases, they were 2–9 years old, and the body weight was 10–23 kg and (17.48±3.09) kg in average; observation group received sevoflurane-propofol-fentanyl anesthesia, there were 21 male cases and 18 female cases, they were 2–10 years old, and the body weight was 10–22 kg and (17.43±3.13) kg in average. Two groups of children were not statistically different in gender, age and body weight distribution (P>0.05), and the study was approved by the hospital ethics committee.

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) with clinical diagnosis of chronic tonsillitis, (2) patients were ≥1 year old; (3) without serious congenital diseases; (4) with normal nerve motor development, and without cognitive or mental abnormalities. Exclusion criteria: (1) associated with systemic infectious diseases; (2) with acute tonsillitis attack; (3) without serious congenital diseases; (4) with normal nerve motor development, and without cognitive or mental abnormalities. Exclusion criteria: (1) associated with systemic infectious diseases; (2) with acute tonsillitis attack; (3) cognitive or mental abnormalities. Exclusion criteria: (1) associated with systemic infectious diseases; (2) with acute tonsillitis attack; (3) without serious congenital diseases; (4) with normal nerve motor development, and without cognitive or mental abnormalities. Exclusion criteria: (1) associated with systemic infectious diseases; (2) with acute tonsillitis attack; (3) who quit studies and were without complete clinical data.

2.3. Anesthesia methods

Both groups of children were fasting for solids and liquids for 6–8 h before operation. After they entered the operating room, ECG monitoring and blood oxygen saturation were connected, the peripheral vein was opened, then anesthesia induction was conducted, and the observation group received anesthesia as follows: sevoflurane inhalation as well as intravenous injection of propofol 2 mg/kg, fentanyl 2 μg/kg and cis atracurium 150 μg/kg to complete the anesthesia induction, and intraoperative propofol 10 mg/(kg · h) and 10 μg/(kg · h) to maintain anesthesia.

2.4. Serum sample collecting and detecting methods

Before anesthesia, before extubation and the recovery period after extubation, 5 mL of peripheral venous blood was collected respectively and centrifuged to separate serum, then enzyme-linked immunosorbent assay kits were used to detect C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, IL-10, cortisol (Cor), norepinephrine (NE), epinephrine (E), free triiodothyronine (FT3), free thyroxine (FT4), renin (PRA), angiotensin II (AT-II) and aldosterone (ALD) levels.

2.5. Statistical analysis

SPSS18.0 software was used to input and analyze data, measurement data analysis between two groups was by t test, analysis among different time points within group was by variance analysis of repeated measures, and P<0.05 indicated statistical significance in differences.

3. Results

3.1. Inflammation activation caused by emergence agitation

Before anesthesia, before extubation and at recovery period, analysis of serum inflammatory mediators CRP, TNF-α, IL-1β, IL-6 and IL-10 between two groups of patients was as follows: (1) before anesthesia and before extubation, the differences in serum CRP, TNF-α, IL-1β, IL-6 and IL-10 levels were not statistically significant between two groups of patients (P>0.05); at recovery period, serum CRP, TNF-α, IL-1β, IL-6 and IL-10 levels of observation group were significantly lower than those of control group (P<0.05); (2) at recovery period, serum CRP, TNF-α, IL-1β, IL-6 and IL-10 levels of both groups were significantly higher than those before anesthesia and before extubation (P<0.05) (Table 1).

Table 1
Comparison of perioperative serum inflammatory mediator levels between two groups of patients (n=39, X±s).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time points</th>
<th>CRP (μg/mL)</th>
<th>TNF-α (ng/mL)</th>
<th>IL-1β (ng/mL)</th>
<th>IL-6 (pg/mL)</th>
<th>IL-10 (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>Before anesthesia</td>
<td>3.9±0.6</td>
<td>29.3±5.2</td>
<td>10.2±1.5</td>
<td>126.5±16.7</td>
<td>78.7±9.2</td>
</tr>
<tr>
<td></td>
<td>Before extubation</td>
<td>4.8±0.7</td>
<td>36.5±5.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12.9±1.7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>150±20.6&lt;sup&gt;s&lt;/sup&gt;</td>
<td>90.3±11.5&lt;sup&gt;s&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>At recovery period</td>
<td>4.7±0.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>48.6±6.1&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>15.3±1.9&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>178.6±27.6&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>106.5±14.2&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Control group</td>
<td>Before anesthesia</td>
<td>4.0±0.7</td>
<td>29.1±4.9</td>
<td>10.5±1.4</td>
<td>128.1±18.7</td>
<td>78.3±9.6</td>
</tr>
<tr>
<td></td>
<td>Before extubation</td>
<td>4.7±0.8</td>
<td>42.1±6.4</td>
<td>15.2±1.9</td>
<td>187.9±22.6</td>
<td>124.5±17.5</td>
</tr>
<tr>
<td></td>
<td>At recovery period</td>
<td>11.4±1.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>60.2±7.8&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>22.6±2.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>287.6±37.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>156.6±19.6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>: compared with control group at the same time point, P<0.05; <sup>b</sup>: compared with same group before anesthesia, P<0.05; <sup>s</sup>: compared with same group before extubation, P<0.05.
3.2. Neuroendocrine change caused by emergence agitation

Before anesthesia, before extubation and at recovery period, analysis of serum stress hormones Cor, NE, E, FT3 and FT4 between two groups of patients was shown in Table 2: (1) before anesthesia and before extubation, the differences in serum Cor, NE, E, FT3 and FT4 levels were not statistically significant between two groups of patients ($P>0.05$); (2) at recovery period, serum Cor, NE, E, FT3 and FT4 levels of observation group were significantly higher than those before anesthesia and before extubation ($P<0.05$). Analysis of serum RAAS system hormones PRA, AT-II and ALD between two groups of patients was shown in Table 3: (3) before anesthesia and before extubation, the differences in serum PRA, AT-II and ALD levels were not statistically significant between two groups of patients ($P>0.05$); (4) at recovery period, serum PRA, AT-II and ALD levels of observation group were significantly lower than those of control group ($P<0.05$); (2) at recovery period, serum Cor, NE, E, FT3 and FT4 levels of both groups were significantly higher than those before anesthesia and before extubation ($P<0.05$).

4. Discussion

Pediatric tonsillectomy requires high quality of anesthesia, which not only requires enough depth of anesthesia to reduce intraoperative operation stimulation to pharyngeal mucosa, but also has to shorten the recovery time after drug withdrawal and make patients recover all sorts of reactions as soon as possible so as to avoid the secretions reflux and airway obstruction caused by postoperative extubation. Both propofol and fentanyl are the general anesthetics with short half-life and rapid metabolism, the recovery is quick after drug withdrawal, but it will increase the risk of emergence agitation to a certain extent[5,6]. Sevoflurane is an inhalational anesthetic used in general anesthesia in recent years, it is with fast induction and recovery, and it can reduce the dosage of muscle relaxants[7]. Study has shown that sevoflurane combined with propofol and fentanyl has improving effect on the emergence agitation after pediatric tonsillectomy, but there is no specific report about the neurohumoral changes caused by emergence agitation[8]. The most direct impact of emergence agitation on the body is the activation of the inflammatory response, which will result in the abnormal secretion of CRP, TNF-$\alpha$, IL-1$\beta$, IL-6 and other pro-inflammatory mediators as well as IL-10 and other anti-inflammatory mediators. In the study, the analysis of the perioperative inflammatory response and inflammatory cytokine levels showed that at recovery period, serum CRP, TNF-$\alpha$, IL-1$\beta$, IL-6 and IL-10 levels of both groups were significantly higher than those before anesthesia and before extubation ($P<0.05$), and serum CRP, TNF-$\alpha$, IL-1$\beta$, IL-6 and IL-10 levels of observation group were significantly lower than those of control group ($P<0.05$). This means that emergence agitation can cause inflammatory reaction activation, and sevoflurane can more effectively reduce the degree of inflammatory response activation at recovery period than ketamine.

Emergence agitation will not only cause the activation of systemic inflammatory response, but can also lead to neuroendocrine system disorder and cause the dysfunction of various endocrine glands and the change of endocrine hormones. Adrenal glands and thyroid gland are the endocrine glands that play an important role in trauma, stress and other pathologic processes, and they are involved in the regulation of energy metabolism changes, hemodynamic changes

### Table 2

Comparison of perioperative serum stress hormone levels between two groups of patients ($n=39, \bar{x}\pm s$).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time points</th>
<th>Cor (ng/mL)</th>
<th>NE (ng/mL)</th>
<th>E (ng/mL)</th>
<th>FT3 (pmol/L)</th>
<th>FT4 (pmol/L)</th>
</tr>
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<tbody>
<tr>
<td>Observation group</td>
<td>Before anesthesia</td>
<td>98.7±10.9</td>
<td>39.5±5.5</td>
<td>29.5±5.1</td>
<td>4.6±0.6</td>
<td>7.2±0.9</td>
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<tr>
<td></td>
<td>Before extubation</td>
<td>114.6±14.5</td>
<td>45.6±7.1</td>
<td>33.4±5.6</td>
<td>5.8±0.9</td>
<td>8.1±1.1</td>
</tr>
<tr>
<td>Control group</td>
<td>Before anesthesia</td>
<td>127.6±16.2</td>
<td>54.2±7.7</td>
<td>39.4±5.2</td>
<td>7.2±0.9</td>
<td>9.0±1.2</td>
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<tr>
<td></td>
<td>At recovery period</td>
<td>130.4±17.6</td>
<td>57.6±8.1</td>
<td>41.5±6.7</td>
<td>7.1±0.9</td>
<td>11.3±1.5</td>
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<td></td>
<td>Before anesthesia</td>
<td>162.1±18.9</td>
<td>78.6±9.8</td>
<td>53.5±7.4</td>
<td>8.9±1.1</td>
<td>13.8±1.9</td>
</tr>
<tr>
<td></td>
<td>At recovery period</td>
<td>99.4±10.7</td>
<td>39.1±6.7</td>
<td>29.1±4.6</td>
<td>4.5±0.8</td>
<td>7.3±0.8</td>
</tr>
</tbody>
</table>

*ab: compared with control group at the same time point, $P<0.05$; *: compared with same group before anesthesia, $P<0.05$; #: compared with same group before extubation, $P<0.05$.

### Table 3

Comparison of perioperative serum RAAS system hormone levels between two groups of patients ($n=39, \bar{x}\pm s$).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time points</th>
<th>PRA</th>
<th>AT-II</th>
<th>ALD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>Before anesthesia</td>
<td>0.91±0.11</td>
<td>276.8±33.2</td>
<td>98.2±10.3</td>
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<tr>
<td></td>
<td>Before extubation</td>
<td>1.14±0.15</td>
<td>296.5±38.6</td>
<td>125.6±16.7</td>
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<tr>
<td>Control group</td>
<td>Before anesthesia</td>
<td>0.93±0.12</td>
<td>325.6±42.6</td>
<td>139.1±18.6</td>
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<tr>
<td></td>
<td>Before extubation</td>
<td>1.45±0.18</td>
<td>279.1±36.7</td>
<td>99.4±10.9</td>
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<tr>
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<td>At recovery period</td>
<td>1.93±0.24</td>
<td>342.1±44.2</td>
<td>154.2±18.9</td>
</tr>
<tr>
<td></td>
<td>At recovery period</td>
<td>1.93±0.24</td>
<td>396.5±51.5</td>
<td>193.3±22.5</td>
</tr>
</tbody>
</table>

*ab: compared with control group at the same time point, $P<0.05$; *: compared with same group before anesthesia, $P<0.05$; #: compared with same group before extubation, $P<0.05$. 
and anti-stress ability changes. The cortisol secreted by adrenal cortex can affect the metabolism of a variety of materials and strengthen the body's anti-trauma and anti-stress ability, the medulla hormones NE and E secreted by adrenal medulla are the important vasoactive substances, have significant vasoconstrictive activity and can guarantee the blood perfusion of important organs during stress and trauma[9-11]. The stress caused by emergence agitation can activate the hypothalamus-pituitary-adrenal cortex axis and increase the secretion of cortisol, and the sympathetic nervous system excitement can increase the secretion of adrenal medulla hormones. The thyroxine secreted by thyroid gland is the important endocrine hormone that regulates energy metabolism, FT3 and FT4 can act on peripheral tissues and then increase the basal metabolic rate, and the stress caused by emergence agitation can activate the hypothalamus-pituitary-thyroid axis and increase the secretion of thyroid hormones[12]. In the study, the analysis of perioperative endocrine function of adrenal gland and thyroid gland showed that at recovery period, serum Cor, NE, E, FT3 and FT4 levels of both groups were significantly higher than those before anesthesia and before extubation (P<0.05), and serum Cor, NE, E, FT3 and FT4 levels of observation group were significantly lower than those of control group (P<0.05). This means that emergence agitation will cause the adrenal and thyroid activation, and sevoflurane can more effectively reduce the change of adrenal and thyroid function at recovery period than ketamine.

Renin-angiotensin-aldosterone system (RAAS) is the endocrine axis that plays an important regulating role in the cardiovascular system, and it has significant impact on water sodium metabolism and vasomotor. Under the action of external stressors, the massive secretion of NE, E and other vasoactive substances caused by stress reaction activation can cause afferent glomerular arteriole contraction and perfusion reduction, which will stimulate the macula densa and trigger massive renin secretion. Renin is the upstream regulating molecule of RAAS system, it can act on angiotensinogen and convert it into angiotensin I, and the latter is split into the regulating molecule of RAAS system, it can act on angiotensinogen in the zona glomerulosa of the adrenal cortex and trigger massive renin secretion. Renin is the upstream regulating molecule of RAAS system, it can act on angiotensinogen and convert it into angiotensin I, and the latter is split into the regulating molecule of RAAS system, it can act on angiotensinogen in the zona glomerulosa of the adrenal cortex and trigger massive renin secretion.

In the study, the analysis of perioperative RAAS system activation showed that at recovery period, serum PRA, AT-II and ALD levels of both groups were significantly higher than those before anesthesia and before extubation (P<0.05), and serum PRA, AT-II and ALD levels of observation group were significantly lower than those of control group (P<0.05). It means that emergence agitation can cause RAAS system activation, and sevoflurane can more effectively reduce the degree of RAAS system activation at recovery period than ketamine. To sum up, it is believed that combined sevoflurane-propofol-fentanyl anesthesia for children with tonsillectomy can improve the emergence agitation and reduce the neuroendocrine change caused by agitation, and the specific characteristic is inhibiting the activation of inflammatory response and stress response.

References


