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LETTER TO THE EDITOR

Effect of Different Depths of Anesthesia on Perioperative Stress Response in Children Undergoing Adenoidectomy and Tonsillectomy

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Children may suffer from perioperative stress response easily due to their special mental and physical characters. The main biological reaction of perioperative stress response is hypothalamic-pituitary-adrenocortical (HPA) reaction, which arouses hyperglycemia, excessive secretion of ACTH, cortisol, somatropin, catecholamines, angiotensin II, glucagon and lactate, and decreases secretion of insulin and testosterone [1]. β-endorphin is a kind of endogenous opioid neuropeptide, studies showed that it relates with children's stress response [2]. In children, the plasma concentration of β-endorphin increases during and after operations. Severe or persistent stress response may cause heart, lung, kidney, and brain damages, immunosuppression or even death. Decreasing perioperative stress response can improve prognosis and reduce hospitalization time [3].

The depth of anesthesia is derived from different doses of intravenous or inhaled anesthetics, assisted by analgetics. Monitoring methods include auditory evoked potentials (AEP), bispectral index (BIS) and spectral edge frequency (SEF), etc. BIS has a good correlation with many anesthetic drugs (such as propofol, midazolam, and sevoflurane, etc.), but the best correlation with propofol [4]. BIS effectively monitors the depth of intravenous anesthesia with remifentanil and propofol in children [5]. Propofol–remifentanil total intravenous anesthesia (TIVA) can be effective in preventing the release of stress hormones during anesthesia and operation [6]. Previous studies have reported the effect of different depths of inhalation anesthesia on perioperative stress response in adult patients [7]. No literature has reported the effect of different depths of TIVA on perioperative stress response. We conducted a prospective, randomized study comparing the effect of different depths of propofol–remifentanil TIVA on perioperative hemodynamics and stress hormones in children undergoing adenoidectomy and tonsillectomy. In this study, we test three common stress hormones: cortisol, β-endorphin, and insulin.

This study protocol was approved by the Ethics Committee of Xinhua Hospital, Shanghai Jiaotong University School of Medicine. Written informed consent was obtained from all children's parents. We studied 54 children aging from 1 to 8 years undergoing adenoidectomy and tonsillectomy. They were randomly (by opening an envelope) allocated to deep anesthesia group (group D, n = 27) or light anesthesia group (group L, n = 27). In group D, BIS was maintained between 25 and 35, while in group L, it was maintained between 50 and 60. The anesthesia induction procedure was same in both groups: midazolam 0.1 mg/kg, remifentanil target-controlled-infusion (TCI) plasma concentration at 2 ng/mL, 2 min later TCI propofol. In group D, endotracheal intubation was performed when BIS reached 35, while in group L when it reached 60. Propofol and remifentanil were used for maintenance of anesthesia in both groups, remifentanil plasma concentration was controlled at 2 ng/mL, propofol plasma concentration was adjusted according to BIS. Propofol and remifentanil were stopped at the end of operation.

In both groups, sex, age, height, body weight, duration of surgery, intubation times, time from end of operation to tracheal extubation, and dosage of propofol were recorded. Each 5-ml peripheral vein blood sample was taken at T0, T1, T2, T3 for measurement of cortisol, β-endorphin and insulin (T0 = before anesthesia; T1 = 5 min after tracheal intubation; T2 = 15 min after operation started; T3 = 5 min after tracheal extubation). β-endorphin concentration was detected by enzyme-linked immunosorbent assay, cortisol, and insulin concentration were detected by

Table 1 Hemodynamic date and stress hormones during the study period

Variables	Group	T0	T1	T2	T3
HR (bpm)	D	107 ± 8.99	97.2 ± 9.11*	98.6 ± 7.58*	107 ± 7.07
	L	106 ± 9.94	99.9 ± 10.6*	101 ± 8.48*	110 ± 8.32
MAP (mmHg)	D	80.2 ± 6.39	67.4 ± 8.27*	69.7 ± 8.19*	77.0 ± 8.45
	L	78.1 ± 7.90	69.6 ± 8.09*	71.3 ± 8.58*	78.1 ± 9.67
Cortisol (μg/dL)	D	15.0 ± 1.80	10.5 ± 1.54*	9.12 ± 1.67*	7.98 ± 1.28*
	L	15.8 ± 2.17	13.2 ± 2.01*, **	11.9 ± 1.87*, **	10.7 ± 1.22*, **
β-endorphin (ng/mL)	D	5.21 ± 1.66	5.56 ± 1.74	5.81 ± 1.95	7.96 ± 1.99*
	L	5.42 ± 1.98	6.20 ± 1.81	6.57 ± 1.61	10.5 ± 1.76*, **
Insulin (UIU/mL)	D	2.48 ± 0.68	2.95 ± 0.89	3.18 ± 0.76	5.19 ± 0.89*
	L	2.52 ± 0.98	2.78 ± 0.79	2.90 ± 0.86	3.82 ± 0.79*, **

HR, heart rate; MAP, mean arterial pressure; BIS, bispectral Index; T0, before anesthesia; T1, 5 min after tracheal intubation; T2, 15 min after operation started; T3, 5 min after tracheal extubation; D group, deep group; L group, light group. Data are mean ± SD. *P<0.05, Compare with T0; **P<0.01 between groups.

DXI800 chemiluminescence immune assay analyzer. Data were statistically analyzed by one-way ANOVA. Level of significance was set at a P-value of 0.05.

There were no significant differences with regard to sex, age, body weight, height, duration of surgery, and the time from end of operation to tracheal extubation in two groups. The dosage of propofol in group D was significantly higher than that in group L ($P < 0.05$).

Cortisol plasma concentrations decreased significantly during anesthesia and operation in both groups (T0 to T1, T2, T3, $P < 0.05$). Comparing with group L, we observed significantly lower cortisol concentration in group D at T1, T2, and T3 ($P < 0.01$). β-endorphin concentration tended to increase during anesthesia and operation in both groups, but showed no significant difference at T1 and T2 (T0 to T1, T2). And after tracheal extubation, it increased significantly in both groups (T0 to T3, $P < 0.05$). Comparing with group L, β-endorphin concentration showed significant lower level at T3 in group D ($P < 0.01$). Insulin concentration increased in both groups, and the changes were similar with β-endorphin. HR and MAP showed no significant difference between two groups at T0, T1, T2, and T3 (Table 1).

It has been proven that propofol can reduce the secretion of cytokine and CRH by inhibiting γ-aminobutyric acid receptors and glutamate receptors, thus decreasing the secretion of cortisol [8]. Opioids have a stronger impact on stress response by inhibiting opioid receptors. Remifentanil, as a new type of ultra-short-acting μ-receptor agonist, has a similar pharmacologic action with other opioids [9]. This study showed that during propofol–remifentanil TIVA, deep anesthesia can produce more effective inhibition on the perioperative stress response. This result accorded with Roizen's study, Roizen et al. [7] found that increasing the depth of halothane anesthesia can significantly decrease the endocrine metabolism stress response during skin cutting.

In conclusion, during propofol–remifentanil TIVA, deep anesthesia can more effectively inhibit the perioperative cortisol reaction, postoperative β-endorphin reaction and postoperative reducing of the insulin concentration in children undergoing adenoidectomy and tonsillectomy. However, in this study, all children underwent adenoidectomy and tonsillectomy, which are minor surgeries with little injury and shot time-consuming. How about the larger surgeries? Further researches need to be done to investigate the impact of different depths of anesthesia on stress hormones in larger or longer time-consuming surgeries.

Acknowledgments

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Conflict of Interest

The authors declare no conflict of interest.

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