

Original Research Article

Effects of different doses of dexmedetomidine on post-surgical emergence agitation and oxidative stress in children

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Abstract

Purpose: To study the effects of various dexmedetomidine (DEX) doses on post-surgical emergence agitation (EA) and oxidative stress in children.

Methods: At various times, mean arterial pressure (MAP) and heart rate (HR) were measured: prior to anesthesia (T0), during intubation (T1), at onset of operation (T2), and at the end of surgery (T3). The incidence of post-surgical EA was estimated, and the extent of agitation were determined based on pediatric anesthesia emergence delirium (PAED). Post-surgical pain was determined using facial pain scale (FPS). Serum levels of cortisol (Cor), epinephrine (E), and norepinephrine (NE) were quantified at T0 and T3. Extubation time and awakening time, as well as postoperative complications were recorded.

Results: At T1, T2 and T3, levels of HR and MAP were significantly increased in all three groups, when compared to the corresponding values at T0, with group C having peak values, followed by A and B. Group B had a lower incidence of EA than groups A and C, but EA incidence was lower in group A than in group C. The lowest scores for PAED and FPS were in group B ($p < 0.05$). Blood levels of Cor, E and NE at T0 were comparable amongst the three groups. However, at T3, serum levels of these parameters were lower in group B than in each of the other 2 groups.

Conclusion: At a dose of 0.5 $\mu\text{g}/\text{kg}$, DEX effectively reduces the incidence of post-surgical EA, improves hemodynamics, and alleviates oxidative stress responses in pediatric anesthesia.

Keywords: Dexmedetomidine, Pediatric anesthesia, Post-surgical emergence agitation, Oxidative stress, Hemodynamics

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INTRODUCTION

Adverse reactions during the peri-extubation period of general anesthesia, especially during pediatric peri-surgical anesthesia, are have continued to receive increasing attention from anesthesiologists and surgeons [1]. Due to their

young age and low body weight, children may cry and be uncooperative prior to surgery [2]. In addition, some children may develop strong stress response because of panic. This may induce hemodynamic fluctuations, and ultimately compromise surgical efficiency. Therefore, the enhancement of safety and quality of awakening

in children during the peri-anesthesia period is a major concern. Currently, combination of intravenous and inhalational anesthesia is widely used for children [3]. Emergence agitation (EA), defined as a state of excitement, agitation, and disorientation, is a common postoperative issue in anesthesia, and it manifests in unconscious movements, crying or moaning, and delusions [4]. Improper treatment of EA may hamper post-anesthesia recovery and endanger the safety of children. The risk factors for EA are age, palinesthesia time, pain and environment. Dexmedetomidine (DEX) is a new and highly selective α_2 adrenergic receptor agonist which exerts analgesic, sedative and anti-anxiety effects [5]. It has 7-fold higher affinity for α_2 receptors than clonidine, with little effect on hemodynamic indices during anesthesia. Postoperative use of DEX in children effectively inhibits stress response and mitigates EA [6]. In this study, children scheduled for elective surgery were given anesthesia using two different doses of DEX, and the effect of the drug on hemodynamics and EA were determined. This was with a view to providing a basis for the use of DEX anesthesia in surgically-treated children.

METHODS

Participants

A total of 110 children who underwent surgery at Weifang Second People's Hospital from February 2019 to May 2020 were recruited and allocated to three groups: low-dose DEX group (group A, $n = 41$, comprising 23 males and 18 females aged 6.7 ± 1.5 years); high-dose DEX group (group B, $n = 38$, consisting of 22 males and 16 females aged 6.6 ± 1.3 years), and control group (group C, $n = 31$, comprising 17 males and 14 females aged 6.4 ± 1.0 years). The protocol used followed international guidelines for human studies, and ethical approval for the study was received from the Ethics Committee of Weifang Second People's Hospital, and all family members signed informed consent form. There were no significant differences in general data amongst the three groups of patients ($p > 0.05$).

Inclusion and exclusion criteria

Inclusion criteria: children aged 3-11 years who were in the category of ASA I or ASA II, took part in this investigation [7].

Exclusion criteria: children with coagulation dysfunction or a history of drug allergy; children with severe heart, lung, liver, and kidney dysfunction, and children with malignant

hyperthermia and mental diseases, were excluded from the study.

Treatments

All children were deprived of food and water for 6 - 8 h. General anesthesia was performed with intramuscular injection of atropine (0.01 mg/kg), and intravenous infusions of midazolam (0.1 mg/kg), propofol (2 mg/kg), and fentanyl (4 μ g/kg). Cisatracurium besylate (0.1 mg/kg) was intravenously infused after loss of eyelash reflex, and anesthesia was maintained with sevoflurane inhalation. Subsequently, children in groups A and group B were given Dex at doses of 0.3 and 0.5 μ g/kg, respectively, while children in group C were given equivalent volume of normal saline in place of DEX. The trachea was extubated after post-surgical awakening.

Hemodynamic parameters

The indexes HR and MAP were measured at T0, T1, T2, and T3.

Evaluation of post-surgical EA

Post-surgical EA was assessed with pediatric anesthesia emergence delirium (PAED) [8]. The PAED consisted of the following five features: ability of children to obey instructions and communicate with caregivers, purposefulness in the behaviour of children, children's awareness of their surroundings, restlessness, and distress/inconsolability. Each item was rated from 0 to 4 on a scale from mild to severe. The total score on the five sub-item scores was taken as the score for agitation during the period of recovery from anesthesia. The higher the score, the greater the possibility of agitation during the recovery period, and the more serious the degree of EA. Scores >11 were taken as positive diagnosis of EA.

Assessment of post-surgical pain

The facial pain scale (FPS) [9] was employed to measure post-surgical pain. The children were made to select from six faces, the face that best matched their pain status viz 0: no pain; 1: occasional pain; 2: pain that did not affect normal activities; 3: pain that prevented patients from prolonged activities; 4: pain that prevented patients from performing activities; and 5: severe pain that prevented free movement.

Determination of oxidative stress factors

At T0 and T3, 3 mL of venous blood samples were taken from each patient. The blood

samples were centrifuged at 1400 rpm for 5 min to obtain sera. Serum levels of Cor, E, and NE were quantified using ELISA.

Evaluation of symptoms and complications

Extubation time and awakening time, as well as the incidence of complications (nausea and vomiting, respiratory depression, hypoxemia, and severe cough), were compared among the three groups.

Statistical analysis

Statistical analysis was carried out with SPSS 21.0. Continuous data are expressed as mean ± SD ($\bar{x} \pm s$). Inter-group comparison was conducted with ANOVA, followed by LSD pairwise comparison test. Counting data are presented as numbers and percentages (n, %), and comparison amongst groups was done with Chi-squared (χ^2) test. Statistical significance of difference was assumed at $p < 0.05$.

RESULTS

Peri-surgical hemodynamic indices

Peri-surgical indices (MAP and HR) were comparable among the three groups at T0 ($p > 0.05$). However, at T1, T2, and T3, the levels of these indices were significantly increased in the

three groups, with the highest level observed in group C, followed by group A, and then group B ($p < 0.05$, Table 1).

Post-surgical PAED scores and incidence of EA

The incidence of EA was reduced in group A (26.8 %), when compared with group C (51.6 %), but higher than that in group B (7.9 %, $p < 0.05$, Table 2).

Extubation time, awakening time and post-surgical pain

Patients in group B had shorter extubation and awakening times than those in groups A and C ($p < 0.05$), but the levels of these parameters were similar in groups A and C. Group B had significantly decreased FPS score for assessing post-surgical pain, relative to groups A and C (Table 3).

Pre- and post-surgical levels of Cor, E and NE

The three groups had no significant differences in terms of levels of serum Cor, E, and NE at T0 ($p > 0.05$). However, at T3, serum levels of Cor, E, and NE were lowest in group B, followed by group A, and then group C ($p < 0.05$, Figure 1).

Table 1: Perisurgical hemodynamic indices in the 3 groups at various times

Variable		T0	T1	T2	T3
MAP (mmHg)	Group A (n = 41)	91.7 ± 8.4	109.7 ± 9.4 ^a	114.4 ± 10.5 ^a	119.5 ± 10.8 ^a
	Group B (n = 38)	91.3 ± 8.0	105.3 ± 9.6 ^{ab}	109.2 ± 10.1 ^{ab}	113.7 ± 11.9 ^{ab}
	Group C (n = 31)	91.6 ± 8.2	111.5 ± 10.4 ^a	118.6 ± 11.1 ^a	124.5 ± 12.1 ^a
HR (beats/min)	Group A (n = 41)	63.4 ± 6.1	71.5 ± 7.1 ^a	74.3 ± 7.2 ^a	76.9 ± 7.8 ^a
	Group B (n = 38)	63.1 ± 6.3	67.2 ± 6.8 ^{ab}	69.1 ± 7.0 ^{ab}	71.6 ± 7.2 ^{ab}
	Group C (n = 31)	63.5 ± 6.0	72.3 ± 7.0 ^a	75.9 ± 7.5 ^a	79.4 ± 7.6 ^a

Values are presented as mean ± SD. ^a $P < 0.05$, vs. T0, ^b $p < 0.05$, vs. groups A and C

Table 2: Post-surgical PAED scores and EA

Variable	PAED score			EA (PAED score >11)
	1-10	11-15	16-20	
Group A (n = 41)	30 (73.2)	8 (19.5)	3 (7.3)	11 (26.8) b
Group B (n = 38)	35 (92.1)	3 (7.9)	0 (0)	3 (7.9) ab
Group C (n = 31)	15 (48.4)	7 (22.6)	9 (29.0)	16 (51.6) a

Results are presented as n (%). ^a $P < 0.05$, vs. group A, ^b $p < 0.05$, vs. group C

Table 3: Extubation time, awakening time, and post-surgical pain ($\bar{x} \pm s$)

Variable	Extubation time (min)	Awakening time (min)	FPS score
Group A (n=41)	11.27 ± 1.15	8.61 ± 0.92	4.26 ± 0.45
Group B (n=38)	10.48 ± 1.03 ab	8.30 ± 0.75 ab	3.52 ± 0.38 ab
Group C (n=31)	11.84 ± 1.18	8.69 ± 0.97	4.46 ± 0.49

^a $P < 0.05$, vs. group A, ^b $p < 0.05$, vs. group C

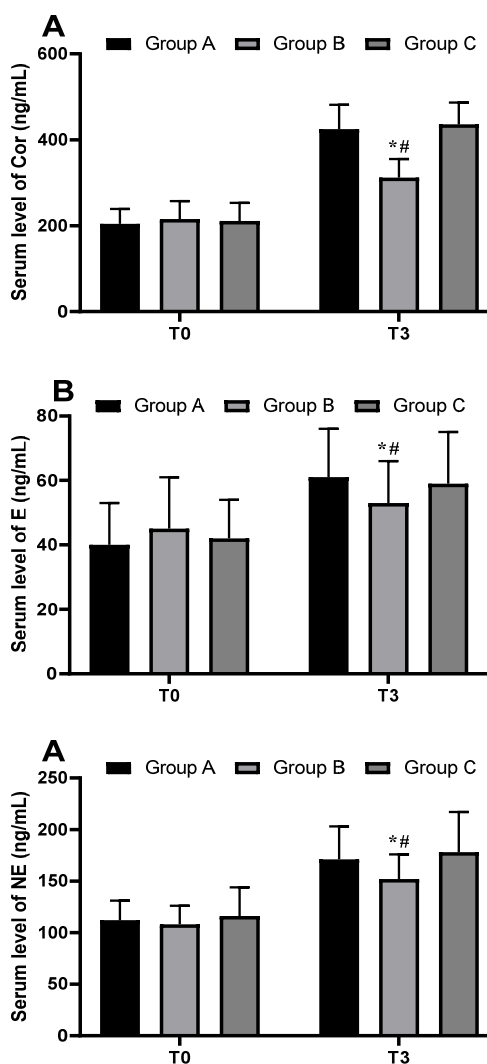


Figure 1: Pre- and post-surgical levels of cortisol, epinephrine and norepinephrine. A: Changes in cortisol levels in the three groups; B: changes in epinephrine levels in the three groups; C: changes in norepinephrine levels in the three groups. * $P < 0.05$, vs. group A; # $p < 0.05$, vs. group C

Incidence of complications

Fewer complications were observed in group B children than in those in groups A and C (5.2 % vs. 22.2 % and 22.4 %, respectively ($p < 0.05$, Table 4).

Table 4: Incidence of complications in the three groups

Variable	Nausea and vomiting	Respiratory depression	Hypoxemia	Severe cough	Overall complication
Group A (n = 41)	3 (6.7)	2 (6.7)	2 (4.4)	2 (4.4)	9 (22.2)
Group B (n = 38)	1 (2.6)	0 (0)	1 (2.6)	0 (0)	2 (5.2) ^{ab}
Group C (n = 31)	2 (6.4)	2 (6.4)	1 (3.2)	2 (6.4)	7 (22.4)

Results are presented as n (%). ^a $P < 0.05$, vs. group A, ^b $p < 0.05$ vs. group C

DISCUSSION

Pediatric patients have underdeveloped organ functions and weak capacities for self-regulation and recovery. Agitation may occur in 10 to 80 % of children at the time of awakening from general anesthesia, thereby prolonging recovery from consciousness and diminishing treatment efficiency [10]. Therefore, sedative and analgesic drugs are necessary for preventing EA after general anesthesia. At present, drugs for treating EA in children include lornoxicam, tramadol and opioids[11]. However, opioids and related sedatives usually produce different degrees of respiratory depression which delay postoperative awakening, making them unsuitable for children [12]. Evidence has shown that DEX antagonizes sympathetic nerve overactivity, downregulates stress response, and mitigates hemodynamic fluctuations during perioperative anesthesia in children [13].

In the present study, the levels of HR and MAP in the three groups were higher during intubation, at onset of operation, and post-operation, than their corresponding pre-anesthesia values. The highest levels of HR and MAP were observed in the group given saline (control group), followed by the low-dose DEX group (0.3 $\mu\text{g}/\text{kg}$), and the high-dose DEX group (0.5 $\mu\text{g}/\text{kg}$). These results indicate that DEX was effective in antagonizing sympathetic nerve overactivity, as well as reducing plasma catecholamine levels, and lowering levels of HR and MAP during the recovery period. Thus, DEX maintained stability of vital signs in the children [14]. The high-dose DEX group (0.5 $\mu\text{g}/\text{kg}$) had the lowest incidence of EA, followed by the low-dose DEX group (0.3 $\mu\text{g}/\text{kg}$), and the saline-treated control group. Moreover, the high dose DEX group (0.5 $\mu\text{g}/\text{kg}$) had shorter extubation and awakening times, as well as lower FPS scores than the low-dose DEX group, but these parameters were similar in the group given DEX at the dose of 0.3 $\mu\text{g}/\text{kg}$ and the saline control group. Therefore, the use of DEX produced a desirable sedative effect and prevented EA during awakening from anesthesia, thereby mitigating fluctuations in vital signs, and reducing postoperative pain.

It has been reported that the *locus coeruleus* is the target of DEX. Arousal response in the cerebral cortex is regulated by noradrenergic fibers in the dorsal bundle from the locus coeruleus [15]. Dexmedetomidine (DEX) reduces the release of the neurotransmitter NE by obstructing the α_2 adrenergic receptors in the presynaptic membrane, thereby weakening the excitability of the postsynaptic membrane and inhibiting arousal response. This property may facilitate the simultaneous restoration of sensation and consciousness, with an analgesic effect, thereby lowering the incidence of agitation. This is consistent with findings in the present study. In addition, there were no significant differences in serum levels of Cor, E and NE amongst the three groups before anesthesia. However, post-surgery levels of Cor, E and NE were lower in the group given DEX at a dose of 0.5 $\mu\text{g}/\text{kg}$ than in the 0.3 $\mu\text{g}/\text{kg}$ DEX group and saline control group. Increased stress response leads to large fluctuations in intraoperative hemodynamics and anesthetic accidents due to intolerance. In this study, DEX was effective in alleviation of post-surgical stress responses in children. Furthermore, patients who received DEX at a dose of 0.5 $\mu\text{g}/\text{kg}$ experienced fewer complications than those given the lower dose of DEX (0.3 $\mu\text{g}/\text{kg}$) or normal saline. In general, surgery in children under general anesthesia is normally performed within a short period of time. Therefore, the use of DEX requires strict dose control, since overdose may lead to complications of delayed awakening.

CONCLUSION

The use of DEX in pediatric surgery reduces the occurrence post-operation EA, improved hemodynamics, and alleviated stress responses in pediatric anesthesia. A higher treatment efficiency is achieved at a DEX dose of 0.5 $\mu\text{g}/\text{kg}$ than at a lower dose of 0.3 $\mu\text{g}/\text{kg}$.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the contents of this article will be borne by the authors. Baofeng Lou and Jing Ren conceived and designed the study, drafted the manuscript, collected, analyzed and interpreted the experimental data,

and revised the manuscript for important intellectual content. Both authors read and approved the final manuscript.

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