

Original Article

Dexmedetomidine in pediatric intravenous general anesthesia without tracheal intubation

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Abstract: Objective: The aim of this study was to investigate the application of dexmedetomidine in pediatric intravenous general anesthesia without tracheal intubation. Methods: From January 2014 to January 2017, a total of 152 children that received intravenous general anesthesia without tracheal intubation, before scheduled surgeries, were recruited in this study. They were divided into an observation group (n=82) and a control group (n=70) by means of a random number table. For children in the observation group, intravenous infusion of dexmedetomidine was administered at 1.0 µg/kg within 10 minutes after initiation of intravenous anesthesia. When complete, the maintaining dose was pumped intravenously at 1.0 µg/kg/h and then propofol at 1-2 mg/kg per hour. The 70 children in the control group received equal doses of normal saline during intravenous general anesthesia. Time for leaving the post-anesthesia care unit (PACT), awakening time, scores on the pediatric anesthesia emergence delirium (PAED) scale, adverse events in the recovery period, heart rates (HR), mean arterial pressure (MAP), serum cortisol, and aldosterone levels at different time points were compared between the two study groups. Results: Time for leaving from the PACT and awakening time of children were insignificantly different between the observation group and control group (P>0.05). PAED scores for postoperative emergence delirium (ED) and incidences of pain and restlessness in the recovery period in the observation group were all remarkably lower than the control group (all P<0.05). At different time points (10 min, 20 min, and 30 min after dexmedetomidine or normal saline pump infusion and at the end of surgery), slower heart rates (HR), higher mean arterial pressure (MAP), and lower cortisol and aldosterone levels of children were noted in the observation group compared to control group (all P<0.05). Conclusion: The application of dexmedetomidine to pediatric intravenous general anesthesia, without tracheal intubation, can lead to stabilization of the circulatory system, relieve stress response, and effectively reduce restlessness and pain during the recovery period. Thus, it is worthy of extensive clinical use.

Keywords: Dexmedetomidine, intravenous anesthesia, non-tracheal intubation, children

Introduction

Recently, the number of children receiving intravenous general anesthesia without tracheal intubation before scheduled surgery is on the rise. However, surgical anesthesia in children is characterized by low stability of the blood circulation system and triggering intense stress response, affecting the quality of anesthesia [1, 2]. Accordingly, higher requirements are made for pediatric anesthesia in a clinical setting. Under existing conditions, it is of clinical implication to improve the quality of intravenous general anesthesia without tracheal intubation to ensure perioperative safety in children, reduce the stress response, and reduce

restlessness and pain during the recovery period.

Currently, agents used for intravenous general anesthesia without tracheal intubation in children primarily include sevoflurane, ketamine, and propofol [3]. Sevoflurane-related pediatric postoperative restlessness is more common [4]. Ketamine has side effects such as restlessness, delirium, hallucinations, increased secretion, and potential neurotoxicity [5, 6]. The use of propofol in intravenous general anesthesia without tracheal intubation in children is associated with high incidence of circulatory and respiratory depression and glossocoma, as well as reduced safety [7]. These drugs are imper-

fect, affecting the quality and safety of pediatric anesthesia. Dexmedetomidine is a highly selective α_2 -adrenergic receptor agonist that has anti-sympathetic, sedative, analgesic, and anxiolytic effects, causing minimal circulatory and respiratory depression [8, 9]. A large number of studies have reported that dexmedetomidine has been administered in combination with the abovementioned sedatives and used in all stages of general anesthesia with endotracheal intubation. It contributes to good sedation, with less stress response during tracheal intubation, reduced use of intraoperative anesthetic agents, while maintaining hemodynamic stability and less respiratory depression [10]. Nevertheless, few reports have been concerned with the use of dexmedetomidine in intravenous general anesthesia without tracheal intubation in children. Therefore, this study aimed to elucidate the effects of dexmedetomidine on recovery quality, circulation, and stress response indexes after intravenous general anesthesia without tracheal intubation in children, providing more clinical evidence for the application of dexmedetomidine in pediatric anesthesia.

Materials and methods

General data

Between January 2014 and January 2017, 152 children that underwent elective herniorrhaphy, in The Affiliated Hospital of Youjiang Medical University for Nationalities, were recruited for this study. Children varied in age from 2 to 7 years, had I-II grade of the American Society of Anesthesiologists (ASA) Physical Status Classification System, and weighed 14-40 kg. The children were randomly divided into an observation group (n=82) and control group (n=70). Children were eligible for enrollment if they received elective herniorrhaphy, had no surgical contraindications, and if the children and their families actively cooperated. Children were excluded if they were accompanied by multiple organ dysfunction syndrome involving the heart, lung, liver, and kidneys; if they were allergic to anesthetics (propofol, midazolam, and dexmedetomidine); if they had a respiratory tract infection within one month before surgery; if they had no central nervous system disease or had not administered sedatives, analgesics, or anesthetics in recent years. All family members of the children recruited into this

study submitted written informed consent. This study was approved by the Medical Ethics Committee of The Affiliated Hospital of Youjiang Medical University for Nationalities.

Anesthetic modalities

Children in both the observation group and control group received intravenous general anesthesia without tracheal intubation. Upon entering the operating room, each child was given an oxygen mask and was monitored for vital signs. Intravenous access was established and oxygen was given. For all children in both groups, initially, an intravenous infusion of midazolam was administered at 0.1 mg/kg and propofol at 2-3 mg/kg. Afterward, intravenous pump infusion of propofol was administered at 1-2 mg/kg/h to maintain anesthesia, followed by intravenous infusion of fentanyl at 1.0 μ g/kg. Lactated Ringer's solution was injected to supplement physiological needs and losses in the intraoperative period. For children in the observation group, an intravenous infusion of dexmedetomidine was administered at 1.0 μ g/kg within 10 minutes after initiation of intravenous anesthesia. When complete, an intravenous pump infusion of dexmedetomidine at 1.0 μ g/kg/h and then propofol at 1-2 mg/kg per hour were given to maintain anesthesia. In contrast, those in the control group received equal doses of normal saline instead of dexmedetomidine.

Outcome measures

Time for leaving the post-anesthesia care unit (PACU) (time from the end of the surgery, stay in the PACU, and return to the ward), awakening time, and scores on the pediatric anesthesia emergence delirium (PAED) scale were compared between the two groups [11]. Emergence delirium (ED) of children was evaluated within 30 minutes after recovery and scored every 5 minutes. The highest scores were utilized as valid monitoring values. Items of the scale included eye contact with caregivers, purposeful actions, awareness of surroundings, restlessness, and inconsolability, with scores for each item ranging from 0 to 4. The scoring criteria for the first three items (eye contact, restlessness and inconsolability, and awareness of the surroundings) were classified into no, a little, some, very, and extremely, with each item scoring from 4 to 0. Scoring criteria for the last two items (restlessness and inconsolability)

Table 1. Baseline characteristics of children

Variables	Case	M/F	Age (year)	Weight (kg)	ASA I/II	Operative time (min)
CG	70	65/5	4.12±1.54	26.4±8.24	37/33	37.85±7.63
OG	82	74/8	4.23±1.61	28.9±7.31	47/35	38.52±8.02
t/ χ^2 value		0.330	0.106	0.134	0.304	0.162
P value		0.566	0.894	0.862	0.581	0.839

Note: M/F denotes male/female; CG, control group; OG, observation group; ASA I/II, I/II grade of the American Society of Anesthesiologists (ASA) Physical Status Classification System.

were classified into no, a little, some, very, and extremely, with each item scoring from 0 to 4. Higher PAED scores indicated more severe ED.

Children in the two groups were also compared regarding incidence of adverse events in the recovery period. These included pain, restlessness, nausea and vomiting, lethargy, bradycardia, and hypotension. Heart rates (HR) and mean arterial pressure (MAP) of children at different time points (before dexmedetomidine or normal saline pump infusion, 10 min, 20 min, and 30 min after dexmedetomidine or normal saline pump infusion, and at the end of surgery) were compared between the two groups. Moreover, serum cortisol and aldosterone levels at different time points were also compared. Blood samples (3 mL each) were drawn from each patient at various time points (before dexmedetomidine or normal saline pump infusion, 10 min, 20 min, and 30 min after dexmedetomidine or normal saline pump infusion, and at the end of surgery). Serum cortisol and aldosterone levels were measured by radioimmunoassay (RIA). The RIA kits were purchased from Sigma, USA, and the procedures of RIA were completed in strict accordance with manufacturer instructions.

Statistical analysis

All statistical data were processed using SPSS software, version 19.0. Measurement data with normal distribution are described as mean \pm standard deviation. Between-group comparisons were conducted with independent samples t-tests and repeated measures analysis of variance (ANOVA) with Bonferroni's post hoc tests were applied to compare indexes at different time points. Rest measurement data were tested by one-way ANOVA. Count data are expressed as percentages and intergroup comparisons were performed with the application

of χ^2 tests. $P < 0.05$ was deemed as statistically significant.

Results

Baseline characteristics of children

Children in the control group and observation group differed insignificantly in age, sex, weight, operative time, and other characteristics at baseline (all $P > 0.05$), as shown in **Table 1**.

Time for leaving PACU and awakening time of children

No remarkable differences were noted in time to leave PACU and awakening time of children between the two groups (both $P > 0.05$, **Figure 1**).

PAED scores of children

PAED scores in the observation group were significantly reduced compared to the control group ($t = 4.524$, $P = 0.043$, **Figure 2**).

Adverse events of children in the recovery period

Rates of pain and restlessness in the recovery period in the observation group were substantially lower than the control group (both $P < 0.05$). Nevertheless, no substantive disparity was observed in rates of vomiting, lethargy, bradycardia, and hypotension between the two groups ($P > 0.05$, **Table 2**).

Values of HR and MAP of children at different time points

Repeated measures ANOVA demonstrated that values of HR and MAP of children were remarkably different at different time points (all $P < 0.005$). HR values of the children at 10 min, 20 min, and 30 min after dexmedetomidine or normal saline pump infusion were higher than before pump infusion. MAP values, however, were lower in both groups. Moreover, lower HR values but higher MAP values were observed in the observation group, compared to control group, at 10 min, 20 min, and 30 min, as well as at the end of surgery (**Table 3**).

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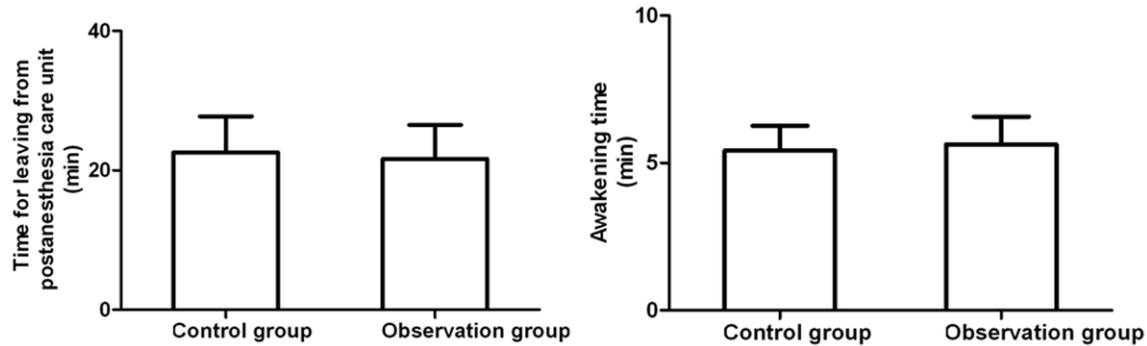


Figure 1. Comparison of time for leaving PACU and awakening time of children between the two groups.

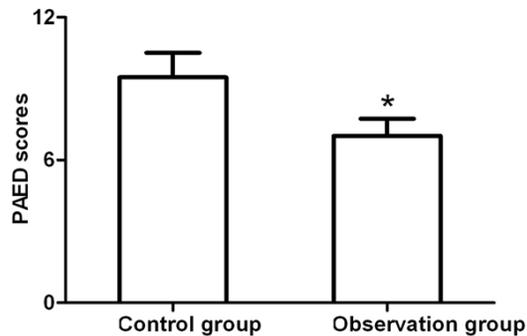


Figure 2. Comparison of PAED scores of children between the two groups. *P<0.05, compared with the control group; PAED denotes the pediatric anesthesia emergence delirium scale.

Serum cortisol and aldosterone levels of children at different time points

Repeated measures ANOVA revealed that cortisol and aldosterone levels at different time points varied strikingly among the children (all P<0.005). Compared with levels before pump infusion, cortisol and aldosterone levels of children increased in both groups at 10 min, 20 min, and 30 min after dexmedetomidine or normal saline injection, and at the end of surgery, respectively. Lower cortisol and aldosterone levels were observed in the observation group than the control group (Table 4).

Discussion

A wide range of factors, including surgical trauma and stress response, affect the quality of intravenous general anesthesia without tracheal intubation in children. How to reduce their stress response and maintain the stability of vital signs is a hotspot of current research [12]. Children undergoing surgery show characteris-

tics of young age, light weight, immature organs, low tolerance to surgical anesthesia, and fluctuating hemodynamics during anesthesia [13]. Intravenous general anesthesia without tracheal intubation, adopted in the present study, can meet the requirements for hernia repairs in children. However, in clinical practice, tracheal intubation is frequently performed during operations due to severe hypoxemia induced by improper depth of sedation or the body's stress response. Dexmedetomidine is a highly selective α_2 -adrenergic receptor agonist that specifically exerts multiple effects (sedation, analgesia, stress relief, and inflammatory response). It is considered an ideal anesthetic adjuvant for stress relief and hemodynamic stabilization [14, 15]. Children with intravenous general anesthesia without tracheal intubation are often associated with diverse degrees of physiological disorders and pathological changes. The results of this current study demonstrated that HR values of children in the control group presented a rapidly increasing trend, but MAP values showed a decreasing trend during anesthesia. Nevertheless, at 10 min, 20 min, and 30 min after dexmedetomidine or normal saline pump infusion, and at the end of surgery, HR values were remarkably lower but MAP values were considerably higher in the observation group than control group (all P<0.05). These results suggest that intravenous infusion and maintenance of dexmedetomidine helps stabilize hemodynamics in children. This could be due to the fact that dexmedetomidine can reduce excitability of sympathetic nerves, induce slower heart rates, activate α_2 -receptors in peripheral vascular smooth muscle cells, and give rise to vasoconstriction and elevated blood pressure. It has positive effects on suppressing HR and enhancing MAP. On the other

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Table 2. Adverse events of children in the recovery period (n, %)

Variables	Case	Pain	Restlessness	Vomiting	Lethargy	Bradycardia	Hypotension
CG	70	18 (25.71)	15 (21.43)	3 (4.29)	5 (7.14)	4 (5.714)	6 (8.57)
OG	82	3 (3.66)	4 (4.88)	4 (4.88)	8 (9.76)	7 (8.54)	7 (8.54)
χ^2 value		13.631	8.005	0.000	0.330	0.126	0.000
P value		<0.001	0.005	1.000	0.566	0.722	0.994

Note: CG denotes control group; OG, observation group.

Table 3. Values of HR and MAP of children at different time points

	Groups	Before injection	10 min after injection	20 min after injection	30 min after injection	End of surgery
HR (time/min)	CG	108.49±7.42	124.24±10.39	126.92±7.84	131.47±5.24	118.96±4.17
	OG	109.14±8.36	113.84±12.47*	115.24±8.06*	121.36±7.04*	110.23±5.16*
P value		0.179	0.046	0.039	0.044	0.012
MAP (mmHg)	CG	72.4±6.64	65.24±5.24	63.37±5.16	61.88±4.72	62.21±6.02
	OG	71.41±6.09	69.32±5.26*	66.63±6.65*	65.47±6.23*	66.47±5.36*
P value		0.284	0.045	0.041	0.037	0.035

Note: CG denotes control group; OG, observation group; *P<0.05, compared to the control group; HR, heart rates; MAP, mean arterial pressure.

Table 4. Cortisol and aldosterone levels of children at different time points

	Groups	Before injection	10 min after injection	20 min after injection	30 min after injection	End of surgery
Cortisol (nmol/L)	CG	481.25±42.48	536.74±50.25	568.72±44.82	607.25±57.41	645.42±61.05
	OG	479.62±27.62	493.47±23.84*	516.25±42.37*	523.84±25.81*	541.74±24.87*
P value		0.364	<0.001	<0.001	<0.001	<0.001
Aldosterone (ng/mL)	CG	0.17±0.08	0.23±0.11	0.24±0.13	0.29±0.15	0.36±0.18
	OG	0.16±0.07	0.18±0.09*	0.19±0.12*	0.23±0.11*	0.27±0.13*
P value		0.352	0.031	0.028	0.015	0.012

Note: CG denotes control group; OG, observation group; *P<0.05, compared to the control group.

hand, dexmedetomidine can lower atecholamine levels in peripheral blood of children and reduce doses of other anesthetic drugs, contributing to the stability of hemodynamics. The results of this study are basically consistent with results reported in previous studies [16, 17].

Under the action of stress, a series of neuroendocrine responses are triggered in the body. The most prominent responses are the release of rich catecholamine induced by excitement of the sympathetic-adrenal medulla system and secretion of adrenocorticotrophic hormones and adrenal corticosteroids by the hypothalamic-pituitary-adrenal cortex [18]. Serum aldosterone and cortisol levels can be utilized as specific indicators for evaluation of stress response and reflect the body's stress state, to some extent. Excessive stress might cause damage

to the body, affect recovery after surgery, and increase perioperative complications. Stress response to surgical trauma exerts a significant effect on children, resulting in release of cortisol and aldosterone into the blood circulation [19]. In his present study, during intravenous general anesthesia without tracheal intubation, cortisol and aldosterone levels of children increased in the control group, implying that stress response was present and intervention was necessary to reduce it. The use of dexmedetomidine greatly downregulated cortisol and aldosterone levels in children in the observation group, indicating that dexmedetomidine can significantly reduce stress response, aligning with results reported by Gu et al. [20].

Pain and delirium in the recovery period are common adverse reactions to intravenous general anesthesia in children, possibly causing

physical injury and threatening the lives of children, if severe [21, 22]. Regarding adverse effects, the results of the present study exhibited no significant differences in vomiting, lethargy, bradycardia, and hypotension between the two groups. Incidence of restlessness and pain, however, were remarkably lower in the observation group than control group, suggesting that dexmedetomidine can significantly reduce incidence of restlessness and pain for children in the recovery period. Additionally, PAED scores of the observation group were considerably lower than the control group, implying that dexmedetomidine is associated with a remarkable reduction in postoperative ED. This might be related to the effects of dexmedetomidine on analgesia, sedation, and anxiolysis.

In conclusion, use of dexmedetomidine in intravenous general anesthesia without tracheal intubation in children aids in favorable stability of blood circulation, reduced stress response, effectively reduced restlessness and pain during the recovery period, and better safety. Hence, it is worthy of extensive clinical use. However, there are some limitations to this study including small sample size, lack of long-term follow ups, and failure to analyze the effects of dexmedetomidine at different doses. Therefore, in future research, multicenter prospective studies with larger sample sizes are required to further clarify the functions and mechanisms of dexmedetomidine in pediatric intravenous general anesthesia without tracheal intubation.

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Disclosure of conflict of interest

None.

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