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Original Article

Different doses of dexmedetomidine in children with non-tracheal intubation intravenous general anesthesia

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Abstract: Objective: To elucidate the clinical efficacy of diverse doses of dexmedetomidine for children who underwent non-tracheal intubation intravenous general anesthesia. Methods: From December 2015 to December 2017, 156 pediatric patients with inguinal hernias who underwent intravenous general anesthesia with non-tracheal intubation in The First Affiliated Hospital of Inner Mongolia Medical University were recruited as participants in this study. The children were subdivided into the low-dose dexmedetomidine group (n=52), the high-dose dexmedetomidine group (n=52) and the control group (n=52) by means of a random number table. At the initiation of anesthesia, the children in the low-dose dexmedetomidine group were given intravenous infusion of dexmedetomidine at 0.5 μg/kg while those in the high-dose dexmedetomidine group were given intravenous dexmedetomidine at 1.0 μg/kg. The two groups were then given intravenous pump infusion of dexmedetomidine at 0.5 or 1.0 μg/kg/h until the end of the surgery. In contrast, the children in the control group were treated with equal doses of normal saline at the beginning of anesthesia. The heart rate (HR), oxygen saturation (SpO_2), and the mean arterial pressure (MAP) values of children were compared among the three groups before dexmedetomidine injection (T0), after completion of dexmedetomidine injection (T1), and at the end of the surgery (T2), respectively. Additionally, adverse events, the degree of sedation, scores on the modified version of the Faces, Legs, Activity, Cry, and Consolability (FLACC) scale, and recovery time were also compared among the three groups. Results: At T1 and T2, lower HR values but higher MAP values were observed in children with low-dose and high-dose dexmedetomidine than in controls. At T1, lower HP value and higher MAP value were noted in the high-dose dexmedetomidine group than in the low-dose dexmedetomidine group. At T2, the HR and MAP values varied insignificantly between children with high-dose dexmedetomidine and those with low-dose dexmedetomidine. The incidence of total adverse events among the three groups was also insignificant, although the incidence of postoperative restlessness was more remarkably decreased in the low-dose dexmedetomidine group and in the high-dose dexmedetomidine group compare to the control group ($P<0.05$). After 5-minute intravenous infusion of dexmedetomidine, the proportions of children with good sedative results differed insignificantly among the children with different doses of dexmedetomidine injection, as well as the recovery time. The FLACC scores were substantially lower in the low-dose dexmedetomidine group and the high-dose dexmedetomidine group than in the control group ($P<0.05$), but showed insignificant disparity in the FLACC scores between children with low-dose dexmedetomidine and those with high-dose dexmedetomidine. Conclusion: Injecting lower doses of dexmedetomidine to children who undergo non-tracheal intubation intravenous general anesthesia is associated with improvements in hemodynamic stability and sedation, declined incidences of restlessness and pain, and better safety profiles in children.

Keywords: Dexmedetomidine, pediatrics, non-tracheal intubation, general anesthesia

Introduction

Pediatric patients have a psychologic status that is extremely unstable due to their age. When undergoing anesthesia and surgeries in the operation room, they are isolated from their parents. In this context, they are prone to become fearful and irritable and difficult to cooperate with. All of this influences the surgical procedures. Therefore, it is necessary to choose an anesthetic technique with the best anesthetic effect and the fewest adverse events [1, 2]. Due to the shorter operation time, some pediatric patients choose intravenous general anesthesia without tracheal intubation. Ketamine is a commonly used anesthetic ag-

ent. The time to onset of action is short, but it frequently gives rise to side effects including hallucination, restlessness, myocardial inhibition, increased secretions and catecholamine release, as well as neurotoxicity, which severely affects the anesthetic effects, perioperative physical and mental health of children, and also impose a certain burden on the guardians of children [3-5]. Therefore, it is essential for anesthesiologists to select an anesthetic adjuvant with few side effects but effective sedative and analgesic effects for such surgical patients.

Dexmedetomidine is a dextroisomer of medetomidine and a potent α_2-adrenoceptor agonist with 8-fold higher activity than clonidine [6, 7]. Dexmedetomidine is a sedative, analgesic, and anxiolytic, and has the advantages of inhibiting impulse transmission in a sympathetic ganglion and maintaining hemodynamic stability, without affecting the respiratory system. With more profound research on general anesthesia before pediatric surgery, preoperative injection of dexmedetomidine has been found to contribute to lower risks for anesthesia and reduced restlessness rates in children during the recovery period. As a result, dexmedetomidine use has caught more attention from researchers [8, 9]. Nevertheless, the optimal dose for dexmedetomidine use has not reported so far [10]. In this study, a total of 104 children with inguinal hernias hospitalized in The First Affiliated Hospital of Inner Mongolia Medical University were recruited as participants to investigate the clinical effects of pre-injection of dexmedetomidine at different doses in children who underwent general intravenous anesthesia with non-tracheal intubation, in hope of providing experimental evidence for the clinical guidance of pediatric anesthesia.

Materials and methods

Study participants

Between December 2015 and December 2017, 156 children with inguinal hernia admitted to The First Affiliated Hospital of Inner Mongolia Medical University were required to undergo surgical treatment and met the indications for non-tracheal intubation for general intravenous anesthesia. In terms of a random number table, they were assigned to receive either intravenous dexmedetomidine for 10 min at 0.5 μg/kg at the initial induction of anesthesia (low-dose dexmedetomidine group, n=52), or intravenous dexmedetomidine for 10 min at 1.0 μg/kg at the initial induction of anesthesia (high-dose dexmedetomidine group, n=52). After injection of the loading dose was completed, the children in the two groups were given intravenous pump infusion of dexmedetomidine at 0.5 or 1.0 μg/kg/h until the end of the surgery. The remaining 52 children were assigned to receive equal doses of normal saline instead of dexmedetomidine or routine anesthesia at the initiation of anesthesia induction (control group, n=52). Children aged from 2 to 6 years old were enrolled in this study if they had no surgical contraindications or if they and their families were actively cooperative with the implementation of this study. Patients were excluded if they were allergic to anesthetic drugs (such as dexmedetomidine) or if they had structural heart defects, the diseases in the central nervous system, mental illness, were overweight or emaciated, had respiratory obstructive disease, mental retardation, hypoevolutism, or severe hepato-renal disorders. This study got approval from the Mental Ethics Committee of The First Affiliated Hospital of Inner Mongolia Medical University, and the legal guardians of the children submitted written informed consent.

Methods

The children had sufficient sleep before surgery, fasted for 6 hours, and were routinely monitored by electrocardiography on entering the operating room. During the surgery, continuous dynamic monitoring was performed for the children's vital signs including the respiratory rates (RR), heart rates (HR), oxygen saturation (SpO_2), and mean arterial pressure (MAP). Intravenous access was constructed and open. Intravenous infusion of midazolam at 0.1 mg/kg and propofol at 2-3 mg/kg were administered. After the injection was completed, intravenous pump infusion of propofol was administered at 1-2 mg/kg per hour to maintain anesthesia, followed by intravenous fentanyl at 1.0 μg/kg. For the children in the high-dose dexmedetomidine group, intravenous infusion of dexmedetomidine was administered for 10 min at 1.0 μg/kg at the initiation of intravenous anesthesia. After the starting dose was completed, intravenous pump infusion of dexme-

Table 1. General data of pediatric patients

Variables	Case	M/F (n)	Age (year)	BMI (kg/m^2)	OT (min)
LDD group	52	30/22	5.1 ± 0.9	14.2 ± 2.1	37.3 ± 7.1
HDD group	52	28/24	4.9 ± 0.6	13.9 ± 2.3	39.1 ± 7.9
Control group	52	31/21	5.0 ± 0.8	13.5 ± 1.9	38.6 ± 7.4
F value/X^2 value		0.366	0.333	0.369	0.348
P value		0.833	0.720	0.696	0.710

Note: LDD group, denotes low-dose dexmedetomidine group; HDD group, high-dose dexmedetomidine group; M/F, male/female; BMI, body mass index; OT, operative time.

Table 2. HR and MAP values of children at different time points

		LDD group	HDD group	Control group	*P* value
HR (time/min)	T_0	108.5 ± 4.3	107.6 ± 3.9	106.4 ± 4.1	0.826
	T_1	90.2 ± 4.2$^{*,\#}$	85.3 ± 2.8$^{*,\#,\Delta}$	108.7 ± 3.6	<0.001
	T_2	105.9 ± 3.1$^{\#}$	106.8 ± 2.9$^{\#}$	113.4 ± 4.4	0.002
SpO_2 (%)	T_0	99.5 ± 0.1	99.4 ± 0.2	99.1 ± 0.3	0.139
	T_1	99.7 ± 0.2	99.5 ± 0.4	99.3 ± 0.5	0.544
	T_2	99.8 ± 0.1	99.7 ± 0.2	99.6 ± 0.2	0.635
MAP (mmHg)	T_0	66.7 ± 4.5	67.2 ± 3.8	68.1 ± 4.3	0.674
	T_1	73.1 ± 3.2$^{*,\#}$	76.9 ± 3.8$^{*,\#,\Delta}$	59.7 ± 2.6	0.004
	T_2	70.2 ± 2.2$^{\#}$	72.7 ± 3.3$^{\#}$	64.4 ± 3.1	0.027

Note: *P<0.05, compared within the same group at T0; $^{\#}$P<0.05, compared with the control group at the same time point; $^{\Delta}$P<0.05 compared with the low-dose dexmedetomidine group. LDD group, denotes low-dose dexmedetomidine group; HDD group, high-dose dexmedetomidine group; HR, heart rate; SpO_2, oxygen saturation; MAP, mean arterial pressure.

detomidine was done at 1.0 μg/kg/h until the end of the surgery. In contrast, those in the low-dose dexmedetomidine group started with 10-minute intravenous infusion of dexmedetomidine at 0.5 μg/kg at the initiation of intravenous anesthesia, followed by maintenance dose of intravenous pump infusion of dexmedetomidine at 0.5 μg/kg per hour until the end of the surgery. The children in the control group were given intravenous infusion of normal saline at equal doses. Through routine clinical observation and assessment, the amounts of other anesthetic drugs were adjusted to maintain suitable depth of anesthesia. The children maintained spontaneous breaths. If the respiratory rate of a child was less than 12 times per minute, manual breathing assistance was necessary.

Outcome measures

The values for HR, SpO_2, and MAP were compared between the children with high-dose dexmedetomidine and those with low-dose dexmedetomidine before injection of dexmedetomidine (T0), at the completion of loading dose of dexmedetomidine (T1), and at the end of surgery (T2). The adverse events (including postoperative restlessness, vomiting, and lethargy) of children were compared among the high-dose dexmedetomidine group, the low-dose dexmedetomidine group and the control group. The degree of sedation was also compared among children in the three groups. The Ramsay Sedation Scale was employed to evaluate different levels of sedation in children: 6 points indicated the child was in fast sleep, and unresponsive, but could be awakened by painful stimulation; 5 points indicated the child was in quiet sleep, and could be awakened by loud shouts; 4 points indicated the child was in light sleep, and was able to respond to a low-voice call quickly; 3 points indicated the child was in a lethargy state, and could respond accurately to commands; 2 points indicated the child was conscious and cooperative and had normal sleep; 1 point indicated the child was anxious. One point represented restlessness, 2-4 good sedation effect, and 5-6 over-sedation. Moreover, the children in the three groups were also compared in postoperative pain and recovery time. The modified version of the Faces, Legs, Activity, Cry, and the Consolability (FLACC) scale was used to assess postoperative pains in children. On the scale, scores varied from 0 to 10, with 0 representing no pain, and 10 representing severe pain.

Statistical analysis

All statistical data were processed with the use of SPSS software, version 18.0. Measurement data with normally distribution are presented as mean ± sd. Comparisons of the indices at different time points were made using repeated-measures analysis of variance (ANOVA) and Bonferroni's post-hoc tests. Other measurement data were tested by one-way ANOVA.

Table 3. Comparison of the incidences of adverse events among children (n, %)

Variables	Case	Restlessness	Vomiting	Lethargy	IAE
LDD group	52	4 (7.69)	2 (3.85)	4 (7.69%)	10/52
HDD group	52	3 (5.77)	3 (5.77)	5 (9.62%)	11/52
Control group	52	11 (21.15)	1 (1.92)	3 (5.77)	15/52
F value		6.774	1.086	0.547	1.517
P value		0.034	0.581	0.761	0.468

Note: LDD group, denotes low-dose dexmedetomidine group; HDD group, high-dose dexmedetomidine group; IAE, incidence of adverse events.

Table 4. Degree of sedation of children (n)

Variables	FLACC score					
	1	2	3	4	5	6
LDD group	7	29	10	6	0	0
HDD group	5	9	31	7	0	0
Control group	9	27	12	4	0	0
X^2 value	1.321					
P value	0.517					

Note: LDD group denotes low-dose dexmedetomidine group; HDD group, high-dose dexmedetomidine group; FLACC, the Faces, Legs, Activity, Cry, and Consolability scale.

Count data are described as percentages, and comparisons across groups were made by the Chi-square tests. P<0.05 was set as statistically significant.

Results

General data of children

No significant disparities were noted in the general data (including gender, age, body mass index (BMI) and operative time) of children among the three groups, and they were comparable (All P>0.05, **Table 1**). All the children completed the surgery successfully.

HR, MAP and SpO_2 values

Repeated-measures ANOVA demonstrated that the HR and MAP values of children differed remarkably at different time points (all P< 0.001), whereas the SpO_2 values were insignificantly different among the children with low-dose dexmedetomidine, those with high-dose dexmedetomidine and controls. The HR values of children were lower, but the MAP values were higher at T1 than those at T0 in children with either low-dose or high-dose dexmedetomidine. Moreover, at T1 and T2, lower HR values but higher MAP values were observed in children with low-dose dexmedetomidine and those with high-dose dexmedetomidine than the controls. At T1, lower HR values but higher MAP values were seen in the children with high-dose dexmedetomidine than in those with high-dose dexmedetomidine (**Table 2**).

Adverse events

There was no significant difference in the incidence of total adverse events among the children with low-dose dexmedetomidine, those with high-dose dexmedetomidine, and the controls. When compared with the control group, the incidence of postoperative restlessness was considerably lower in children with either low-dose or high-dose dexmedetomidine (P<0.05), but the incidence of restlessness varied insignificantly between the children with low-dose dexmedetomidine and those with high-dose dexmedetomidine (**Table 3**).

Degree of sedation of children

The depth of intraoperative anesthesia was satisfactory in all groups. After 5 minutes of intravenous infusion of dexmedetomidine, 43 patients had good sedative effect in the control group, 45 in the low dose dexmedetomidine group and 47 in the high dose dexmedetomidine group, with insignificant disparities in the degree of sedation among the three groups (X^2=1.321; P=0.517; **Table 4**).

Doses of propofol use of children in different groups

The doses of propofol were (72.4 ± 8.5) mg in the low-dose dexmedetomidine group, (48.7 ± 6.3) mg in the high-dose dexmedetomidine group, and (107.4 ± 10.6) mg in the control group. Compared to the control group, the doses of propofol were substantially lower in the low-dose dexmedetomidine group and the high-dose dexmedetomidine group (P<0.0001). The dose of propofol use was declined markedly in the high-dose dexmedetomidine group versus the low-dose dexmedetomidine group (P<0.001; **Table 5**).

Postoperative pain and recovery time of children in the three groups

There was no marked disparity in the recovery time among the three groups. The FLACC

Table 5. Doses of propofol of children among the three groups (mg)

Variables	Case	Propofol
LDD group	52	72.4 ± 8.5
HDD group	52	48.7 ± 6.3
Control group	52	107.4 ± 10.6
F value		27.482
P value		<0.001

Note: LDD group, denotes low-dose dexmedetomidine group; HDD group, high-dose dexmedetomidine group.

Table 6. FLACC pain scores and recovery time (n ± s)

Variable	Case	FLACC score	Recovery time (min)
LDD group	52	2.9 ± 0.8	5.3 ± 1.4
HDD group	52	2.2 ± 0.5	5.7 ± 1.8
Control group	52	4.3 ± 0.9	4.8 ± 1.2
F value		6.053	0.276
P value		0.036	0.768

Note: LDD group denotes low-dose dexmedetomidine group; HDD group; high-dose dexmedetomidine group; FLACC, the Faces, Legs, Activity, Cry, and Consolability scale.

scores of the children with low-dose and high-dose dexmedetomidine were strikingly lower than those of controls, but the scores differed insignificantly between the children with low-dose dexmedetomidine and those with high-dose dexmedetomidine (**Table 6**).

Discussion

Non-tracheal intubation intravenous general anesthesia is applicable for short-term pediatric surgeries, such as appendectomy, hernia repair, hypospadias repair, orchidopexy for testicular descent, and high ligation of processus vaginalis. Non-tracheal intubation intravenous general anesthesia is associated with faster anesthesia, smaller damages, and no risks for asphyxia arising from dislocation of the tracheal tube when compared to tracheal intubation intravenous general anesthesia. Due to immature mental development and poor self-control, pediatric patients are prone to being resistant to and fearful of anesthesia and surgery, and difficult to cooperate with. It is necessary to select an anesthetic adjuvant drug with small side effects, rapid onset of action, and potent sedation and analgesia [11, 12]. Dexmedetomidine is highly selective α_2-adrenergic receptors, which activates the G protein on postsynaptic α_2-adrenergic receptors in the solitary nucleus. In such case, epinephrine release is inhibited. As a result, electrochemical signals are abnormally conversed in the sympathetic nervous system, nerve impulses cannot be transmitted normally, but it does not significantly affect the parasympathetic nervous system. This indirectly increases suppression on the sympathetic nerves, thereby achieving the sedative, analgesic, and anxiolytic effects, but exerting few impacts on the respiratory and circulatory systems. Moreover, it effectively maintains hemodynamic stability, minimizes visceral ischemia and injuries, and provides protection for visceral organs [13, 14]. Previous studies have been primarily focused on dexmedetomidine use in adult surgeries [15, 16]. However, few reports have elucidated the efficacy of dexmedetomidine use in pediatric surgeries, particularly in the efficacy of dexmedetomidine use in non-intubation intravenous general anesthesia. Internationally, the recommended dexmedetomidine use ranges in dose from 0.25 to 0.75 μg/kg per hour in children with mechanical ventilation [17]. However, the optimum dose for dextromethorphan use in non-tracheal intubation intravenous general anesthesia remains unclear. Accordingly, we conducted this study to compare the efficacy of pre-injection of different doses of dexmedetomidine in children with non-tracheal intubation intravenous general anesthesia. The selected children were strictly controlled at the age of 2-6 years. The low dose of dexmedetomidine injection was 0.5 μg/kg, and the high dose 1.0 μg/kg. Furthermore, the enrolled children were randomized into groups. No significant disparity was found in the basic data among children in the three groups, which minimizes the influence of the children's own factors on the results of this study.

Numerous trials have been shown that dexmedetomidine can be utilized as a preoperative anesthetic adjuvant in children and achieve the purpose of pain relief [18]. Another study stated that dexmedetomidine considerably reduced the incidence of restlessness during the recovery period and postoperative adverse reactions in children [19]. Different doses of dexmedetomidine can produce diverse degrees of sedation and analgesia in patients. Within a

certain dose range, higher doses of dexmedetomidine injection contribute to more significant effects [20]. The results of the present study demonstrate that compared with controls, children's HR values were remarkably lower but the MAP values were significantly higher after pre-injection of different doses of dexmedetomidine. At the end of the surgery, the HR and the MAP values differed insignificantly between children with low-dose dexmedetomidine and those with high-dose dexmedetomidine, indicating that low-dose dexmedetomidine use is associated with effective maintenance of hemodynamic stability. Differences in the incidence of total adverse events of children were insignificant among the low-dose dexmedetomidine group, the high-dose dexmedetomidine group and the control group, implying that dexmedetomidine is safe as an anesthetic adjuvant. Dexmedetomidine effectively reduced the incidence of postoperative pain and restlessness in patients after non-tracheal intubation intravenous general anesthesia, and the efficacy was insignificantly different between low-dose dexmedetomidine use and high-dose use. As far as the degree of sedation, no substantive difference was noted in the sedative effects among the high-dose dexmedetomidine group, the low-dose dexmedetomidine group, or the control group. Additionally, the recovery time was unchanged. However, the dose of propofol in the high-dose dexmedetomidine group was strikingly lower than that in the low-dose dexmedetomidine group, and the later was also remarkably lower than that in the control group, suggesting that the insignificant impacts of different doses of dexmedetomidine use on sedation and recovery time of children might be attributed to the decrease of propofol dose.

In conclusion, after investigating the clinical efficacy of pre-injection of different doses of dexmedetomidine in children undergoing intravenous general anesthesia without tracheal intubation, we found dexmedetomidine to be an effective anesthetic adjuvant for sedation and analgesia. It relieved restlessness and pain in children during non-tracheal intubation intravenous general anesthesia, maintained hemodynamic stability, and had favorable safety profiles. Pre-injection of dexmedetomidine at 0.5 μg/kg was more effective than at 1.0 μg/kg. Hence it is worthy of extensive clinical use. Nevertheless, there are still some limitations in this study. For example, the sample size was mall, it was a single-center study, and outcome measures were not diversified. Therefore, in future research, additional multi-center randomized studies with larger sample sizes are required for further validation.

Disclosure of conflict of interest

None.

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