Application of pre-injection of dexmedetomidine of different doses in pediatric intravenous general anesthesia without tracheal intubation

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Abstract. This study observed the clinical efficacy of pre-injection of dexmedetomidine of different doses before surgery and the adverse reactions during the recovery period in pediatric intravenous general anesthesia without tracheal intubation. Pediatric patients who received general anesthesia without tracheal intubation before surgery from January 2016 to March 2017 were randomly divided into four groups (n=30), and were respectively treated with intravenous pump infusion of loaded dexmedetomidine of high-dose (2.5 μg/kg), middle-dose (1.5 μg/kg) and low-dose (0.5 μg/kg), while the children in the control group received injection of normal saline in same dose. Then, the mean arterial pressure (MAP) at different time points (5 and 10 min after administration, after anesthesia and after surgery), heart rate, Ramsay sedation score changes and adverse reactions during recovery period of anesthesia of pediatric patients were compared among four groups. At 5 and 10 min after administration, Ramsay scores of high-dose group and middle-dose group were higher than that of the control group, and the differences had statistical significance (P<0.05). There was no significant difference in comparison of Ramsay scores between low-dose group and the control group. The MAP and heart rate after anesthesia and after surgery of pediatric patients with pump infusion of dexmedetomidine in the three groups were decreased significantly compared to those of the control group, and the differences had statistical significance (P<0.05). The incidence rate of adverse reaction of pediatric patients during the recovery period after pump infusion in the three groups and the control group was, respectively, 13/30, 8/30, 7/30 and 8/30, and the differences were statistically significant (P<0.05). The sedative effect and safety of pre-injection of dexmedetomidine in pediatric intravenous general anesthesia without tracheal intubation are promising, and the medium dosage can maximize the anesthetic effect with less side effects.

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Introduction

As one of the major methods in clinical anesthesia, intravenous general anesthesia without tracheal intubation is used in surgeries of both adult and pediatric patients. It is widely used not only in minor surgeries in superficial area, upper limb, and abdomen, especially hypogastrium of pediatric patients, but also for pediatric pre-medication in prevention of postoperative agitation, compound anesthesia, sedation of pediatric ICU, sedation of pediatric medical imaging and other auxiliary examinations (1,2). With a high selectivity, dexmedetomidine, an agonist of α-2 adrenergic receptor' specificity, is commonly used in clinical sedation, analgesia and anti-anxiety, and has features of stable hemodynamics (3,4) and respiratory non-inhibition (5). Additionally, with this specific characteristic, dexmedetomidine is attracting increased attention of clinical specialists and widely used in clinical sedation of pediatric non-tracheal general anesthesia. The purpose of this study was to observe the effect of dexmedetomidine in different doses applied in pediatric intravenous general anesthesia without tracheal intubation at different time points and the adverse reactions during the recovery period of anesthesia, in order to provide new ideas on anesthesia for clinical pediatric intravenous general anesthesia without tracheal intubation.

Patients and methods

Patients. One hundred and twenty pediatric patients undergoing intravenous general anesthesia without tracheal intubation before surgery from January 2016 to March 2017 were chosen for this research. Inclusion and exclusion criteria: i) the weight of patients was within 15% of the standard weight; ii) pediatric patients were diagnosed without a history of diabetes, hypertension, severe organ diseases, mental diseases, or abnormal anesthesia surgeries; iii) The American Society of anesthesiologists (ASA) grades of pediatric patients were distributed in grade I to II; iv) patients and their families signed the informed

Table I. Comparison of the basic situation of the pediatric patients in each group.

Group	Case (n)	Sex (male/female)	Average age (years old)	Average weight (kg)	Surgery time (min)
Low-dose group	30	14/16	2.5±0.6	12.7±0.5	54±6
Middle-dose group	30	16/14	2.7±0.6	12.6±0.6	56±5
High-dose group	30	17/13	2.4±0.6	12.5±0.4	57±6
Control group	30	15/15	2.6±0.6	12.6±0.7	55±3
Statistics		F=0.112	F=1.43	F=1.98	F=1.26
P-value		0.996	0.256	0.232	0.293

consent and this study was approved by the Ethics Committee of the People's Hospital of China Three Gorges University. All pediatric patients were randomly divided into four groups (n=30). There were 15 male and 15 female patients, aged from 1 to 5 years with an average of 2.6±0.6 years in the control group; 14 cases of male and 16 scases of female patients, aged from 1 to 5 years with and average of 2.5±0.6 years in the low-dose group; 16 cases of male and 14 cases of female patients, aged from 1 to 5 years with an average of 2.7±0.6 years in the mid-dose group; 17 cases of male and 13 cases of female patients, aged from 1 to 5 years with an average of 2.4±0.6 years in the high-dose group. After the general data of patients among the four groups were analyzed by statistical software, there were no significant differences (P>0.05), and the difference had no statistical significance, which indicated that the general data of patients among the four groups were comparable (Table I).

Methods. Patients were required to refrain from food for 6-8 h and water for 4-6 h before surgery. On the day of surgery, peripheral venous access was prepared in the ward using TCI-III type of microelectronic pump (SLGO) via intravenous infusion of dexmedetomidine (batch number: H20090248, production of Jiangsu Hengrui Medicine Co., Ltd. Lianyungang, China). The concentrations of dexmedetomidine in low-dose, mid-dose and high-dose groups were respectively 0.5, 1.5 and 2.5 μg/kg, and diluted to 10 ml with normal saline. Then, dexmedetomidine in different concentrations was injected at a rate of 4 ml/min via venous pump while same amount of saline was injected at 4 ml/min via vein in the control group at the same time. At different time points (5 and 10 min after administration, after anesthesia and after surgery), heart rates of patients were monitored by electrocardiogram monitor (ECG) (Philips Inteli MP70 ECG monitor; Philips, Amsterdam, The Netherlands) and blood pressure (including systolic and diastolic blood pressure) of patients was monitored by pressure monitoring sensor (Shenzhen Yixin Medical New Technology Co., Ltd. Shenzhen, China). Thereafter, the value of MAP was calculated with the formula, MAP = (Systolic pressure + Diastolic pressure x 2)/3, so as to assess the sedative effect of patients. Simultaneously, assessment was carried out using Ramsay score and adverse reactions including nausea, vomiting, restlessness, chills, bradycardia, respiratory depression, and hypotension. during anesthesia recovery period was observed carefully (6). Ramsay scoring criteria (Sobriety of level 1, patients are anxious, restless and agitated; Sobriety of level 2, patients possess good oritentation ability and cooperate quietly or well; Sobriety of level 3, patients respond only to commands; Sleep of level 4, patients react quickly to tap on the glabella or strong-sound stimulus; Sleep of level 5, patients react slowly to tap on the glabella or strong-sound stimulus; Sleep of level 6, patients have no response to tap on the glabella or strong-sound stimulus. Adequate sedation, level 2 and 3 in Ramsay score).

Observation index. For pediatric patients in four groups, we monitored and recorded MAP and heart rates at 5 and 10 min after administration, after anesthesia and after surgery, and observed the degree of sedation and adverse reactions during the recovery period of anesthesia at the same time.

Statistical analysis. The relevant experimental data were statistically processed and analyzed with statistical software of SPSS 13.0 (version X; IBM Corp., Armonk, NY, USA). And the measurement data was expressed as mean ± SD, the enumeration data were tested by Chi-square test, and the comparisons among groups were carried out with single-factor analysis of variance. If the variance was not equal and the data were in normal distribution, t-test would be used, otherwise the non-parametric test would be used. P<0.05 was considered to indicate a statistically significant difference.

Results

Comparison of MAP and heart rate of pediatric patients between the experimental groups and the control group. When compared with the control group, MAP and heart rate at 5 and 10 min after pump infusion of dexmedetomidine, after anesthesia and after operation of all pediatric patients in other three groups were lower and the differences were statistically significant (P<0.05). At 10 min after anesthesia, the comparison of MAP and heart rate after surgery and after anesthesia between the low-dose group and the mid-dose group were statistically significant. The differences of comparison between any two groups at remaining different time points were not statistically significant (Tables II and III).

Comparison of Ramsay scores of pediatric patients in the three groups of different doses and the control group. At 5 and 10 min after administration, Ramsay scores of high-dose and mid-dose group were higher than that of the control group, and there were statistical differences (P<0.05). The differences of

Table II. Comparison of MAP of pediatric patients at different time points (mmHg).

Group	5 min	10 min	After surgery	After anesthesia	P-value
Low-dose	49.4±4.6	52.1±4.2	56.7±4.4	50.6±5.7	<0.01
Middle-dose	48.5±4.7	47.5±5.5	48.3±4.0	48.3±4.1	<0.01
High-dose	47.2±5.1	46.5±5.0	46.2±4.9	46.2±5.6	<0.01
Control	63.5±3.8	65.4±3.6	69.5±4.5	67.3±4.2	

At 10 min after anesthesia, after surgery and after anesthesia, MAP is compared between the low-dose group and the mid-dose group, t=2.14, 3.12 and 1.68, P=0.048, 0.032 and 0.098.

Table III. Comparison of heart rates (bpm) beats per minute of pediatric patients at different time points.

Group	5 min	10 min	After surgery	After anesthesia
Low-dose group	102.4±3.7	99.8±5.3	94±3.8	94±4.8
Middle-dose group	99.5±3.3	96.2±3.1	93.1±4.1	92.2±3.8
High-dose group	96.3±3.5	92.4±4.2	90.2±4.0	90.8±3.4
Control group	127.2±5.1	125.9±5.4	116.6±5.8	122.3±5.0
Statistics	F=3.45	F=3.12	F=3.38	F=5.46
P-value	0.036	0.041	0.039	0.022

At 10 min after anesthesia, after surgery and after anesthesia, the heart rates of pediatric patients in low-dose group and mid-dose group are compared, t=2.56, 3.42 and 1.89, and P=0.042, 0.026 and 0.087.

Table IV. Comparison of Ramsay scores (n).

Grouping by time point	Group	One point	Two points	Three points	Four points	Five points	Six points
5 min after injection	Low-dose	4	17	6	3		
	Middle-dose	0	3	19	5	3	
	High-dose	0	3	18	4	5	
	Control	5	16	7	2		
10 min after injection	Low-dose	3	15	7	5		
	Middle-dose	0	3	9	10	5	3
	High-dose	0	3	7	12	4	4
	Control	4	14	8	4		

comparison of Ramsay scores between the high-dose and the mid-dose groups were not statistically significant (P>0.05). There were no significant differences in comparison of Ramsay scores between low-dose group and the control group (Table IV).

Comparison of the adverse reaction rates during the anesthesia recovery period between the three groups with different doses and the control group. The adverse reaction rate of pediatric patients with pump infusion of dexmedetomidine during the recovery period in the three groups and the control group were respectively 13/30, 8/30, 7/30 and 8/30, and the differences were statistically significant (P<0.05). In pairwise comparison, the adverse reaction rates in the low-dose group were compared respectively with that in the control, the mid-dose and the high-dose groups, and the differences were statistically significant (P<0.05) while the adverse reaction rates of the mid-dose and the high-dose groups, the mid-dose and the control group, the high-dose and the control group were compared, the differences had no statistical significance (P>0.05) (Table V).

Discussion

As a novel and specific α-2 adrenergic receptor agonist, dexmedetomidine can activate the α-2 adrenergic receptor on

Table V. Comparison of adverse reaction rates during the period of anesthesia recovery.

Group	Total (n)	No. of adverse reactions	Adverse reaction rate
Low-dose group	30	13	13/30
Middle-dose group	30	8	8/30
High-dose group	30	7	7/30
Control group	30	8	8/30
Statistics			χ^2=8.54
P-value			0.031

the postsynaptic membrane of the ganglion, the presynaptic adrenergic receptor in the ganglion and avoid the excitation of postganglionic sympathetic nerve by inhibiting the release of adrenaline from preganglionic neurons through the negative feedback mechanism (7,8). After drug administration, it results in a sedative effect similar to that of natural sleep by directly acting on the locus coeruleus (9). Since dexmedetomidine plays a role in sedation and analgesia through these mechanisms, it has been used as premedication for pediatric anxiolytic and analgesic (10-12). Compared with other drugs with the effects of sedation and analgesia, dexmedetomidine has little effect on respiratory system either for children or adults (13,14). The effect of dexmedetomidine on hemodynamics in children is similar to that in adults, such as hypotension and bradycardia, but this does not mean that it has clinical significance (15). Thus, we adopted dexmedetomidine as the drug in this study.

There are relatively few studies on pharmacokinetics of dexmedetomidine in pediatric patients, and when dexmedetomidine is given to pediatric patients via vein, it mainly combines with plasma proteins (16). A report of retrospective study on sedation over 24 h of dexmedetomidine used in pediatric patients indicated that within 0.1-2.5 g/kg/h of dexmedetomidine dose range, there were no obvious adverse reactions in pediatric patients in more than 30 days (17), and when oral concentration of dexmedetomidine was 2.6 μg/kg, sedative effect could be attained within 20 or 30 min for 80% of the pediatric patients (18). Therefore, the safety of the drug is very high in this concentration range. However, when dexmedetomidine was given in slow infusion of more than 30 min, the incidence rate of hypotension was significantly lower (19). Intravenous administration of dexmedetomidine in 0.5 μg/kg could reduce the airway response and cardiovascular response in patients during tracheal extubation (20,21). Therefore, according to the data reported above, we adopted concentration of dexmedetomidine drug dose in the four groups was 0.5 μg/kg for the low-dose group, 1.5 μg/kg for the mid-dose group and 2.5 μg/kg for the high-dose group.

The main objects of this study were pediatric patients, whose ages were strictly controlled between 1 and 5 years. The basic data among four groups showed no significant difference in statistical analysis and were comparable. Randomization in grouping was used to minimize the difference between the experimental groups.

The results showed that at 5 and 10 min after the children were given the drug, the Ramsay scores in the high-dose group and the mid-dose group were higher than that in the control group, and there were statistically significant differences (P<0.05). The Ramsay score in the low-dose group was not significantly different from that in the control group. The MAP and heart rate of the pediatric patients of dexmedetomidine infusion after anesthesia and after surgery in the three groups were significantly lower than that in the control group, and there were statistically significant differences (P<0.05), while no significant statistical difference existed in comparison of the adverse reaction rate among pediatric patients with infusion of dexmedetomidine during the recovery period in the three groups with different doses and the control group.

Deficiencies: The sample size in this experiment was relatively small, and the reliability of the experimental results could be increased by expanding the sample size. Moreover, the observation indicators could be more diversified, such as supplementing the monitor of oxygen saturation, which would make the experiment more convincing and practical.

In conclusion, the sedative effect and the safety of preinjection of dexmedetomidine in pediatric intravenous general anesthesia without tracheal intubation are promising, and the medium dosage can maximize the anesthetic effect with less side effects, which is expected to provide new ideas on anesthesia for clinical pediatric intravenous general anesthesia without tracheal intubation.

Competing interests

The authors declare that they have no competing interests.

References

1. Vilo S, Rautiainen P, Kaisti K, Aantaa R, Scheinin M, Manner T and Olkkola KT: Pharmacokinetics of intravenous dexmedetomidine in children under 11 yr of age. Br J Anaesth 100: 697-700, 2008.
2. Yuen VM, Hui TW, Irwin MG and Yuen MK: A comparison of intranasal dexmedetomidine and oral midazolam for premedication in pediatric anesthesia: A double-blinded randomized controlled trial. Anesth Analg 106: 1715-1721, 2008.
3. Koroglu A, Teksan H, Sagir O, Yucel A, Toprak HI and Ersoy OM: A comparison of the sedative, hemodynamic, and respiratory effects of dexmedetomidine and propofol in children undergoing magnetic resonance imaging. Anesth Analg 103: 63-67, 2006.
4. Haselman MA: Dexmedetomidine: A useful adjunct to consider in some high-risk situations. AANA J 76: 335-339, 2008.
5. Yang XH, Bai Q, Lv MM, Fu HG, Dong TL and Zhou Z: Effect of dexmedetomidine on immune function of patients undergoing radical mastectomy: A double blind and placebo control study. Eur Rev Med Pharmacol Sci 21: 1112-1116, 2017.
6. Martin E, Ramsay G, Mantz J and Sum-Ping ST: The role of the alpha2-adrenoceptor agonist dexmedetomidine in postsurgical sedation in the intensive care unit. J Intensive Care Med 18: 29-41, 2003.
7. Chrysostomou C and Schmitt CG: Dexmedetomidine: Sedation, analgesia and beyond. Expert Opin Drug Metab Toxicol 4: 619-627, 2008.
8. Cormack JR, Orme RM and Costello TG: The role of alpha2-agonists in neurosurgery. J Clin Neurosci 12: 375-378, 2005.
9. Kamibayashi T and Maze M: Clinical uses of alpha2 - adrenergic agonists. Anesthesiology 93: 1345-1349, 2000.
10. Isik B, Arslan M, Tunga AD and Kurtipek O: Dexmedetomidine decreases emergence agitation in pediatric patients after sevoflurane anesthesia without surgery. Paediatr Anaesth 16: 748-753, 2006.

11. Sato M, Shirakami G, Tazuke-Nishimura M, Matsuura S, Tanimoto K and Fukuda K: Effect of single-dose dexmedetomidine on emergence agitation and recovery profiles after sevoflurane anesthesia in pediatric ambulatory surgery. J Anesth 24: 675-682, 2010.
12. Olutoye OA, Glover CD, Diefenderfer JW, McGilberry M, Wyatt MM, Larrier DR, Friedman EM and Watcha MF: The effect of intraoperative dexmedetomidine on postoperative analgesia and sedation in pediatric patients undergoing tonsillectomy and adenoidectomy. Anesth Analg 111: 490-495, 2010.
13. Hosokawa K, Shime N, Kato Y, Taniguchi A, Maeda Y, Miyazaki T and Hashimoto S: Dexmedetomidine sedation in children after cardiac surgery. Pediatr Crit Care Med 11: 39-43, 2010.
14. Al-Zaben KR, Qudaisat IY, Al-Ghanem SM, Massad IM, Al-Mustafa MM, Al-Oweidi AS, Abu-Halaweh SA, Abu-Ali HM and Saleem MM: Intraoperative administration of dexmedetomidine reduces the analgesic requirements for children undergoing hypospadius surgery. Eur J Anaesthesiol 27: 247-252, 2010.
15. Czaja AS and Zimmerman JJ: The use of dexmedetomidine in critically ill children. Pediatr Crit Care Med 10: 381-386, 2009.
16. Petroz GC, Sikich N, James M, van Dyk H, Shafer SL, Schily M and Lerman J: A phase I, two-center study of the pharmacokinetics and pharmacodynamics of dexmedetomidine in children. Anesthesiology 105: 1098-1110, 2006.
17. Mason KP, Zurakowski D, Zgleszewski S, Prescilla R, Fontaine PJ and Dinardo JA: Incidence and predictors of hypertension during high-dose dexmedetomidine sedation for pediatric MRI. Paediatr Anaesth 20: 516-523, 2010.
18. Zub D, Berkenbosch JW and Tobias JD: Preliminary experience with oral dexmedetomidine for procedural and anesthetic premedication. Paediatr Anaesth 15: 932-938, 2005.
19. Chu CS, Cheng KH, Lee KT, Lin TH, Lee ST, Su HM, Voon WC, Sheu SH and Lai WT: Tolerability of ramipril 10 mg daily in high-risk cardiovascular patients in Taiwan: Experience from Kaohsiung Medical University Chung-Ho Memorial Hospital. Kaohsiung J Med Sci 21: 511-516, 2005.
20. Kumari K, Gombar S, Kapoor D and Sandhu HS: Clinical study to evaluate the role of preoperative dexmedetomidine in attenuation of hemodynamic response to direct laryngoscopy and tracheal intubation. Acta Anaesthesiol Taiwan 53: 123-130, 2015.
21. Kothari D, Tandon N, Singh M and Kumar A: Attenuation of circulatory and airway responses to endotracheal extubation in craniotomies for intracerebral space occupying lesions: Dexmedetomidine versus lignocaine. Anesth Essays Res 8: 78-82, 2014.