Int J Clin Exp Med 2015;8(12):22550-22556
www.ijcem.com /ISSN:1940-5901/IJCEM0014879

Original Article

Effects of dexmedetomidine versus propofol on SPO_2 in children with tetralogy of fallot during anesthesia

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Received August 22, 2015; Accepted November 24, 2015; Epub December 15, 2015; Published December 30, 2015

Abstract: Objective: To determine effects of DEX versus propofol on saturation of pulse oximetry (SPO_2) in children with Tetralogy of Fallot (TOF) during anesthesia. Methods: 54 children with TOF who planned to receive corrected operation were randomly assigned to two groups: group DEX and group Propofol. Indicators were compared at T0 (immediate induction of anesthesia), T1 (tracheal catheterization), T2 (skin incision), T3 (sternal exposure) and T4 (aortic catheterization). Results: In group DEX, the hear rate (HR) and partial pressure difference between alveolar air and arteries [$P(A\text{-}a)O_2$] at T1 were lower than those at T0, while systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP) and SPO_2 at T1 were higher than those at T0, with statistically significant differences ($P<0.05$, respectively). In the group Propofol, SBP, DBP, MBP and SPO_2 at T1 were lower than those at T0, while $P(A\text{-}a)O_2$ at T1 was higher than that at T0, with statistically significant differences ($P<0.05$, respectively). There were statistically significant differences in all indicators at T1 between two groups ($P<0.05$, respectively). The group DEX had lower HR and $P(A\text{-}a)O_2$, and higher SBP, DBP, MBP and SPO_2 than group Propofol. There were no statistically significant differences in all indicators (except for lower HR) at other points between two groups. Conclusion: During induction of anesthesia, DEX was better than propofol to improve alveolar oxygenation, reduce myocardial oxygen consumption, increase arterial oxygen content and induce stable induction in patients with TOF, though they were comparable during maintenance of anesthesia.

Keywords: Tetralogy of fallot, dexmedetomidine, propofol, anesthesia

Introduction

Tetralogy of Fallot (TOF) is a complicated congenital heart disease that accounts for the most of cyanotic congenital heart diseases (CCHDs). The anatomical deformities include septal defect, right ventricular hypertrophy, pulmonary stenosis and dextropositioned aorta. The anatomical characteristics may cause spasm of outflow tract of right ventricle under stresses such as strong emotion that increase consumption of oxygen, augmentation of right to left shunt, reduction of circulatory blood oxygen and even anoxia. During anesthesia, potential reduction in systemic pressure can also cause increased right to left shunt in patients with TOF, thereby resulting in reduced peripheral blood oxygen. Therefore, patients are susceptible to low cardiac output syndrome during and after operation. These patients have hemodynamics different from patients with left to right shunt, have poorer heart function and are more likely to develop adverse reactions.

The pharmacological properties of dexmedetomidine (DEX) result in special pharmacological characteristics such as slower heart rate and higher blood pressure during loading dose of DEX. Some experiments demonstrated that administration of DEX in patients with myocardial infarction lowered heart rate to reduce oxygen consumption, thereby reducing mortality. To our knowledge, the use DEX in children with congenital heart disease has been focused on its effect on hemodynamics. Seldom studies reported its application in patients with right to left shunt, especially in patients with TOF. Considering DEX's effects to slow heart rate and increase blood pressure, we designed the study to compare DEX with propofol on hemodynamics and alveolar oxygenation in patients with TOF, and discussed whether it was appropriate to use DEX.

Materials and methods

Subjects

A total of 54 children with TOF (grade II-III by ASA) who selected elective curative surgery were included in the study. Informed consent was obtained from each subject's guardian, after the receiving approval of the experimental protocol by the Human Ethics Committee of our hospital. This study follows the principles of Helsinki Declaration. All children underwent standard arterial catheterization before operation for the purpose to monitor operation and anesthesia. All subjects received relevant physical and laboratory examinations before admission to operation room. The subjects should not meet any of the following exclusion criteria: a, The subject had a history of cardiac conduction system disease (e.g. 1st or 2nd degree AV block) or channelopathy (e.g. long QT). b, The subject was taking digoxin, alpha-adrenergic or beta-adrenergic agonist or antagonist (e.g., clonidine, propranolol, albuterol), anti-arrhythmic medications, or vasodilators (e.g. ACE inhibitors); c, The subject had received a dose of any other active cardiovascular drug within 48 hours; d, The subject was allergic to or had a contraindication to any of the drugs used in the study; e, The subject had Trisomy 21 (exaggerated risk of bradycardia); f, The subject had severe coarctation of the aorta (risk of exaggerated vasoconstriction); g, The subject had Moyamoya disease (risk of recurrent stroke).

Induction of anesthesia

54 children with TOF who planned to receive elective surgery under extracorporeal circulation on the morning were randomly assigned to two groups according to randomization number. The children with odd number were included in the group DEX while those with even number were included in group Propofol. Subjects were anesthetized based on induction protocol. All of them were fasted for food for 6 hours and drinks for 4 hours. Half an hour before admission to the operation room, subjects were orally administered with 0.5 $mg{\cdot}kg^{-1}$ midazolam for sedation. 15 min after lying in a flat position in the operation room, subjects were given with sevoflurane with a volume fraction of 0.05 and fresh air containing 40% O_2 through mask and connected with ECG. Saturation of pulse oximetry (SPO_2), invasive blood pressure (ABP), and partial end-tidal carbon dioxide pressure ($PetCO_2$) were determined at T0 point. Children in group DEX were intravenously administered with 0.2 $mg*kg^{-1}$ midazolam followed by loading dose of 0.5 $mg*kg^{-1}$ DEX within 10 min. When completely asleep, they were intravenously administered with a single dose of 2 $mg*kg^{-1}$ sufentanil followed by 0.6 $mg*kg^{-1}$ rocuronium. Subjects in group Propofol were intravenously administered with 0.2 $mg*kg^{-1}$ midazolam followed by loading dose of 2 $mg*kg^{-1}$ propofol and 2 $mg*kg^{-1}$ sufentanil. When completely asleep, they were intravenously administered with 0.6 $mg*kg^{-1}$ rocuronium. The tracheal catheter was advanced into the subjects under laryngoscope after induction of conscious loss by anesthesia, and connected with anaesthetic ventilator which was equipped with anaesthetic to maintain appropriate anesthesia. The pressure controlled ventilation (PCV) was given with tidal volume of 8-12 $ml*kg^{-1}$ and ventilation frequency of 20-30 times/min (adjusted based on age and weight), and inspiratory/expiratory ratio of 1:1.5-1:1.2. The ventilation parameters were also adjusted based on $PetCO_2$ level, which maintained at 35-45 mmHg.

Maintenance of anesthesia

Appropriate anesthesia was maintained by intravenous and inhaled administration in combination with individualized monitoring and adjustment according to the process of operation and individual responses. Children in group DEX were infused with DEX at a rate of 0.5 $mg*kg^{-1}*h^{-1}$ until the end of extracorporeal circulation, inhaled with 2%~3% sevoflurane complemented with fresh air containing 40% O_2 at a flow rate of about 2 $L*min^{-1}$, intravenously infused with 2.5 $\mu g*kg^{-1}*min^{-1}$ sufentanil to ease pain and 0.6 $mg*kg^{-1}*h^{-1}$ rocuronium to relax muscle. Children in group Propofol received the same treatments as group DEX except for continuous infusion with 3 $mg*kg^{-1}*h^{-1}$ propofol to maintain appropriate sedation. During the whole process of operation, the vital signs such as heart rate and blood pressure were stable. Also, unstability due to operation and other factors reduced. The vital signs of the subjects were under controlled within ±20% of the baseline of their age. During surgeries, dosage of anesthetics was adjusted

Table 1. Demographics of children in two groups (N=54)

Group	Boy/Girl	Age (month)	Height (cm)	Weight (kg)	BSA (m^2)
DEX	16/11	18.6±5.1	82.5±15.8	13.2±3.2	0.45±0.12
Propofol	18/9	19.3±6.2	85.9±18.6	13.8±4.3.	0.46±0.13

Note: BSA: base surface area.

according to different responses of children to surgeries, such as single bolus of 2 ug/kg sufentanil, 0.6 mg/kg rocuronium, etc. After opening up of arteries, patients in both groups were given 5 ug/kg/min dopamine regularly; however, the dosage was adjusted or added with 0.02 mg/kg/min epinephrine or other kinds of drugs according to post-operative cardiac functions. After cardiopulmonary bypass and ultrafiltration, protamine was given at a dosage of 1.5 times of heparin sodium as an antagonism as well as 20 mg/kg calcium gluconate; and 20 UI/kg Human Prothrombin Complex (PPSB) was given to supply coagulation factors. After surgeries, all patients were intubated endotracheally, and sent to Cardiac Intensive Care Unit with vasoactive agents at original dosages. Besides, all these patients were equipped with respirators and other monitors (ABP, EKG, SPO_2, $PetCO_2$, TEM and so on). After revival, patients got regular echocardiography, supine cheat X-ray at bedside. During stays in Cardiac Intensive Care Unit, patients were given 0.02 ug/kg/h sufentanil as an analgesia, 1 ug/kg/h dexmedetomidine as sedation, as well as correspondence vasoactive agents. After achieving stable systemic functions, patients were subjected to extubation after 24 h, and sent to general words after 48 h.

Monitoring indicators

Children in two groups were recorded for $PetCO_2$, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), SPO_2 at T0 (immediate induction of anesthesia), T1 (tracheal catheterization), T2 (skin incision), T3 (sternal exposure) and T4 (aortic catheterization) using multi-functional monitor (Date-Ohmeda, USA). Changes of indicators including partial pressure difference between alveolar air and arteries [$P(A\text{-}a)O_2$], SpO_2, partial pressure of carbon dioxide in artery ($PaCO_2$) and partial pressure of oxygen in artery were analyzed using arterial blood gas analyzer. The demographics were recorded and compared between two groups. The left ventricular ejection fraction (LVEF) and diameters of left and right pulmonary artery at pulmonary bifurcation were determined using biplane two-dimensional ultrasound with Philips Sonos-5500 ultrasound at a frequency of 7.510 MHz. The severity of TOF was determined by calculation of NAKATA index and systolic pressure of the right ventricle.

Statistical analysis

The measurement data was analyzed for normal distribution with the Shapiro-Wilk test using Excel 6.0 and SPSS 19.0 statistical software. The results were reported as mean ± standard deviation if normal distribution was met. Indicators at different points in one group were compared to determine correlation between repeated measurement data. Repeated measurement data were not correlated with a *P*-value of > 0.05 by Mauchly's Test of Sphericity. These data met the requirement of Huynh-Feldt and were analyzed by one-way analysis of variance (ANOVA). Repeated measurement data were correlated if *P* value was less than 0.05, and were analyzed using ANOVA. The comparison of measurement data between two groups were performed using one-way ANOVA. Enumeration data were analyzed using the Chi-square test. Data were statistically significant with a *P* value of less than 0.05.

Results

Comparison of general conditions between two groups

There were 27 patients in each group respectively with a male:female ratio of 2:1. The age of these patients concentrated at 1.5 years old, weight at 13 kg, and body surface area at 0.45 m^2. There were no statistically significant differences in gender, age, weight, height, and body surface area between two groups, with *P* values of more than 0.05, respectively, as shown in **Table 1**. Although all the patients had severe congenital heart diseases, they all developed normally due to case selection. Thus, there were similar difficulties of anesthesia in both groups. The anesthesia and operation were successfully performed in all subjects.

Table 2. Disease severity of children in two groups (N=54)

Group	LVEF (%)	Nakata index (mm^2/m^2)	Pressure of RV (mmHg)	Velocity of MPA (m/sec)	Size of VSD (cm)
DEX	63.6±5.8	201.5±32.1	45.6±8.9	3.99±1.01	0.82±0.21
Propofol	65.3±8.9	197.3±34.2	46.2±4.5	4.25±1.13	0.78±0.22

Note: RV: right ventricle; MPA: main pulmonary artery; VSD: ventricular spetal defect.

Comparison of disease severity between two groups

As shown in **Table 2**, there were no statistically significant differences in LVEF, NAKATA and systolic pressure of right ventricle between two groups, with *P* values of more than 0.05, respectively, demonstrating that the disease severity was similar in two groups. LVEF before surgeries was more than 60% in both groups, which belonged to normal range. Nakata index concentrated at 200 mm^2/m^2, which is suitable for radical surgeries when over 120 mm^2/m^2, indicating that development of left and right pulmonary arteries were similar in both groups. Pressure of right ventricular was relatively high (45 mmHg), and flow velocity was also relatively high (4.0 m/sec), indicating that infundibulum of outflow tract of right ventricular was relatively narrow, which is consistent with characteristics of TOF. Diameter of defects in ventricular spetal defect was about 0.8 cm in both groups, which indicated similar conditions in both groups. Thus, patients from both groups were comparable.

The comparison of monitoring indicators at different points between two groups was shown in **Table 3**. Basic signs [HR, SBP, DBP, MBP, $PetCO_2$, etc.] of children in both groups were almost normal. SPO_2 was over 80%; and baseline value of $P(A\text{-}a)O_2$ was greater than that in general children, which were consistent with TOF children admitting fresh air containing 40% O_2. At T1, SBP, DBP and MBP in group DEX exceeded baseline values by more than 10 mmHg significantly; SPO_2 was over 90%; $P(A\text{-}a)O_2$ decreased around to 150 mmHg; and $PetCO_2$ remained unchanged. However, at T1, SBP, DBP and MBP in group Propofol were significantly lower than baseline values by more than 10 mmHg; SPO_2 decreased to about 70%; $P(A\text{-}a)O_2$ increased to about 235 mmHg; and $PetCO_2$ remained unchanged. During surgeries, HR in group DEX was 80-90 beats/min, which is lower than 120-130 beats/min in group Propofol.

Discussion

The incidence of TOF ranks first in CCHD, accounting for 11% of congenital heart disease [1]. The blockage in the outflow tract of right ventricle is dynamic and dependent on muscular narrowing of funnel. It is correlated with the concentration of catecholamine in the body. During induction of anesthesia, increased consumption of oxygen, lower BH and increased $PaCO_2$ of all causes will worsen muscular spasm of the funnel and cause anoxia event, resulting in worse left to right shunt and vicious circle. DEX, a dexmedetomidine isomer, is a specific agonist for elective alpha-2 adrenergic receptor (α2AR). The effects such as sedation, hypnosis and antianxiety of DEX are medicated by central α2AR that mainly targets locus coeruleus [2, 3]. EBERT [4] and Belleville [5] found that young patients or healthy volunteers developed transient biphase cardiovascular reactions including higher blood pressure and slower heart rate after infusion with 1 μg/kg DEX, probably due to activation of α2B receptor on vascular smooth muscle. To our knowledge, the studies of DEX used in anesthesia of patients with congenital heart disease have focused on sedation and hemodynamics. Seldom studies reported DEX in patients with TOF. Almost no study investigated the effects of DEX on PVR, SVR, Qp:Qs and oxygenation. Propofol (Diprivan), mainly used in the operating arena for induction or maintenance of general anesthesia, is a potent sedative and hypnotic anesthetic. It is titrated to desired clinical effects via continuous intravenous (IV) infusion. Its rapid onset of action (30-45 seconds) facilitates titration and minimizes over sedation. Hypotension is an adverse effect with higher doses. Transient hypertension has been seen during the loading dose with its peripheral vasoconstrictive effects [6]. Therefore, we compared DEX with propofol on SVR and observed changes of oxygenation between two groups.

We also found increased MBP in children who received loading dose. However, there was only

Table 3. Comparison of monitoring indicators at different points between two groups (N=54)

Group	Time	SBP (mmHg)	DBP (mmHg)	MBP (mmHg)	SPO_2	P(A-a)O_2 (mmHg)	HR	$ETCO_2$ (mmHg)	$PaCO_2$ (mmHg)
DEX (n=27)	T0	76.5±18.2	54.5±14.8	67.8±16.7	82±8.6	195.6±45.7	125±23.7	29.9±3.2	39.8±5.2
	T1	89.2±17.6*,†	65.7±19.5*,†	79.6±21.5†,*	92±9.4*,†	150.1±60.5*,†	79±10.2*,†	31.7±4.1	34.5 ±5.1*,†
	T2	78.4±19.6	53.5±14.3	65.8±18.5	94±8.1†	168.8±56.5†	88±21.1*,†	32.8±3.7	38.6 ±4.6
	T3	76.7±21.8	55.8±20.3	66.2±25.7	95±7.6†	163.2±61.2†	91±18.7*,†	30.25±4.6	39.2 ±4.2
	T4	75.2±22.1	57.2±20.1	69.7±24.8	96±8.8†	165.5±58.7†	76±23.7*,†	32.27±5.8	38.7±3.7
Propofol (n=27)	T0	77.2±21.9	51.8±15.6	68.1±22.3	81±12.2	189.3±57.9	118±28.7	31.28±3.2	37.9±5.9
	T1	65.1±20.6†	43.2±13.5	54.8±17.3	73±9.7†	235.2±64.8†	124±12.9	32.15±3.8	39.5±4.7
	T2	74.8±21.1	54.3±15.6	65.7±22.8	94±10.4†	170.8±53.2†	110±15.7	29.57±5.2	38.2±3.6
	T3	81.6±24.8	53.7±16.2	67.3±24.8	95±6.4†	168.9±66.9†	125±25.5	31.25±4.2	36.5±3.7
	T4	76.9±23.4	54.9±15.8	68.6±20.1	96±8.1†	163.5±56.4†	131±32.5	33.86±4.8	37.7±3.9

Footnotes: As shown in the table, children in group DEX had lower HR throughout the observation period. There was no statistically significant difference in HR at T0 compared with other points in group Propfol during observation). There were significant differences in HR at other points (except for T0) between two groups during observation. For other monitoring indicators, there was significant difference (just at T1 point) between groups. During maintenance with drugs, two groups had higher SPO_2 and lower P(A-a)O_2 compared with baseline. *indicated statistically significant difference between two groups. †indicated statistically significant difference between T0 and other points in one group. SBP: systolic blood pressure, DBP: diastolic blood pressure, MBP: mean blood pressure (MBP); SPO_2: saturation of pulse oximetry; P(A-a)O_2: partial pressure difference between alveolar air and arteries; HR: hear rate; $PetCO_2$: partial end-tidal carbon dioxide pressure; $PaCO_2$: partial pressure of carbon dioxide in artery.

increased BP instead of biphase changes in BP. The HR was continuously slowed. Sinus heart rate was observed in the EKG. No adverse reactions such as A-V conduction blockage, sinus arrest and prolonged QT were observed in all subjects. There were no statistically significant differences in MBP and SPO_2 at other points during maintenance of doses between two groups. Although MBP was mildly unsf in two groups and HR was lower in group D, there was no clinical significance. Hence, no treatment was used. Meanwhile, inhibition of impulse delivered by anterior and lateral cells of spinal cord decreased tension of sympathetic nerve, leading to hyperreflexia of vagus and inhibition of sympathetic baroreceptor reflex. After infusion with DEX, plasma concentration of noradrenaline significantly reduced [7]. During induction, the groups D had significantly higher SPO_2 and lower $P(A\text{-}a)O_2$ than group Propofol, indirectly demonstrating increased MBP reduced right to left shunt. There was no difference in $EtCO_2$, suggesting there were no differences in pulmonary ventilation and gas exchange function between two groups. Blood gas analysis showed group DEX had lower $PaCO_2$ than group Propofol, further demonstrating reduction in right to left shunt from the other perspective. Increased perioperative sympathetic activity often leads to rapid HR and high blood pressure. The use of α2 agonist can result in stable hemodynamics, reduce myocardial ischemia and myocardial oxygen consumption. No change in S-T was observed on EKG, suggesting clinical dosage would not increase chance of myocardial ischemia but reduce myocardial oxygen consumption with slower HR, especially used in patients with cyanotic heart diseases such as TOF. A review that analyzed 31 randomized controlled studies including a total of 4,578 patients showed adrenergic α2 agonists markedly decreased overall mortality and myocardial infarction, especially for patients during cardiovascular surgery. Riker *et al* [8] and Carroll [9] reported that the adverse effects of DEX included bradycardia and hypotension. A Meta analysis showed loading dose and maintenance using high dose might induce substantial bradycardia [10]. Some study suggested use of DEX had no impact on heart rate and blood pressure. A study of Bejian et al [11] observed no significant changes in heart rate, blood pressure, SPO_2 and breath in children before and after use of DEX. However, we found HR was markedly lower in group DEX during the whole study. During loading dose, MBP in group DEX was increased first, and then gradually lowered at other points and ultimately returned to the baseline. The difference between our results and those of previous studies might be explained by different dosage. DEX had no inhibition of breath and resulted in lower HR and higher SPO_2 in children with TOF, suggesting DEX reduced oxygen demand of subjects with TOF, which was consistent with results of Venn *et al* [12].

In this study, no significant differences in other indicators except in HR were observed at other points between two groups, suggesting DEX had similar hemodynamics to propofol during anesthesia. Two groups had significantly better SpO_2 and P $P(A\text{-}a)DO_2$ values compared with baseline throughout the observation, which may be explained by other factors such as improved pulmonary oxygenation and respiratory function by ventilator rather than drugs. Additionally, DEX reduced plasma catecholamine concentration and definitely reduced resistance of pulmonary and peripheral vessels. In this study, MBP was lower while SPO_2 was not. Meanwhile, Hammer et al [13] indicated that DEX potentially might prevent elevations in PVR by providing sedation and analgesia without respiratory depression. Based on the evidence, we speculated DEX might not increase PVR, or even more effectively decrease PVR.

There were some limitations in this study. First, the changes in heart functions (such as EF and SV) and pulmonary artery blood flow were not compared between two groups during anesthesia. Therefore, the shunt could not be accurately estimated. Second, the effects on coronary blood flow and myocardial metabolism at different points were not assessed between two groups. Therefore, the impact on myocardial blood flow remained unknown. Third, drugs used in group DEX were not equivalent to those in group Propofol, which resulted in superficial interpretation of results.

Conclusion

In conclusion, DEX is an ideal option for children with TOF undergoing induction of anesthesia during operation. It is better than propofol

to improve the ratio of pulmonary to systemic blood flow (Qp/Qs) and SpO_2, and reduce oxygen demand. DEX is not widely used in children with congenital heart disease during anesthesia since it is used in off-label way, which remains to be further studied.

Disclosure of conflict of interest

None.

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