The Effects of Dexmedetomidine Prescription in Paediatric Patients With Pulmonary Hypertension Under Congenital Heart Surgery

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Abstract- Anesthetized patient management for pediatric patients with pulmonary arterial hypertension (PAH) is a major challenge. The aim of this study was to evaluate the ability of dexmedetomidine to reduce pulmonary arterial hypertension in patients with pulmonary arterial hypertension undergoing cardiac surgery. Sixty-six patients with pulmonary arterial hypertension underwent the study. Patients were randomly divided into two groups: group D received a dexmedetomidine injection in a dose of 1 μg/kg in the first hour and then decreased to 0.5 μg/kg/hr, injection continued after surgery until extubation in the post-anesthetic care unit (PACU). Group C received normal saline 0.9% in a similar volume. Pulmonary artery systolic pressure (PASP) and systemic systolic blood pressure (SSBP) were recorded during and after the surgery in the post-anesthetic care unit. Needing vasodilators, sedatives, extubation time, and the length of ICU stay were recorded for all patients. Patients in the dexmedetomidine group showed a significant reduction in Pulmonary artery systolic pressure and Pulmonary artery systolic pressure/systemic systolic blood pressure rates during surgery and during the first 24 hours in the post-anesthetic care unit (P<0.001). The dexmedetomidine group, in comparison with the control group, needed a significantly lower dose of a vasodilator (P<0.001) and a lower dose of sedation (P<0.001). It is concluded that the use of dexmedetomidine during the surgery in children with pulmonary hypertension reduces pulmonary artery systolic pressure during and after the surgery.

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Introduction

The high pulmonary arterial pressure (PAP) is decreased sharply during the intrauterine period after birth. This high PAP continues for the first 2 to 6 weeks of life, and then it tends to stagnate (1). At about three months of age, a mean pulmonary arterial pressure (mPAP) ≥25 mm Hg for people living at sea level is considered as Pulmonary Hypertensive (PH). Generally, the incidence of PH in children is idiopathic or associated with congenital heart disease (CHD) (2,3). Pulmonary arterial hypertension (PAH) associated with CHD is a subset of the high incidence of PH, which is increased by 5±28% in the last decade (4). Management of PAH during CHD surgery is a difficult and risky task for the surgical team. The main goal of PAH control during surgery is to avoid hypoxemia, hypercapnia, pain, hyperthermia, and hypovolemia. All of these aforementioned factors are related to pulmonary hypertension in response to sympathetic stress that increases pulmonary vascular resistance (PVR) (5). Patients with increased PVR are, therefore, more likely to suffer from a progressive increase in PVR after heart surgery despite cardiac repair (1). Using ventilation strategies to provide adequate oxidation and prevent acidosis, analgesia, adequate relaxation, and optimal hematocrit levels are several methods used to manage this challenge. The drug administration of these patients includes inhalation of nitric oxide, phosphodiesterase type 5 inhibitors (Sildenafil), prostacyclin analogs (epoprostenol), and Indicators (Milrinone) (6). Dexmedetomidine is a specific and selective α two

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adrenergic agonists with rapid tissue distribution and short half-life (7). Dexmedetomidine's effect of reducing hyperdynamic responses (increase in heart rate and blood pressure) and weakening cardiovascular responses in children with pediatric cardiac surgery has been proven (8,9). However, there is only limited information available on the effect of dexmedetomidine on pulmonary arteries and PVR. The aim of this study was to evaluate the ability of dexmedetomidine in reducing pulmonary arterial hypertension in children with congenital heart disease (CHD) who underwent cardiac surgery.

Materials and Methods

This study was conducted at the Faghihi Cardiovascular Research Center affiliated to Shiraz University of Medical Sciences. After obtaining the ethical approval from the independent ethics committee (IEC) and getting informed consent of parents, 66 children with CHD and PAH who were candidates for congenital cardiac surgery underwent the study consecutively (aged 1 to 18 months and weighing more than 2 kg). Diagnosis and confirmation of the patient's PH were performed before the surgery using echocardiography. Patients were randomly assigned into two groups using the computer-generated randomized sequence: the dexmedetomidine (Group D) (n=33) and the control groups (Group C) (n=33).

The study drug was prepared by an independent anesthetist. Therefore, all anesthesia personnel was blinded to therapeutic groups, and in order to maintain consistency, the medical team (cardiovascular surgeons, cardiac anesthesia, and cardiologist) and the post-surgical approach remained consistent throughout the period of the study.

Induction of anesthesia was performed using midazolam 0.05 mg/kg, fentanyl 5μ/kg, and rocuronium 0.2 mg/kg. Radial artery Cannulation for monitoring the invasive blood pressure, non-invasive blood pressure was measured every 2 minutes. After tracheal intubation, dexmedetomidine infusion was started in group D patients in a dose of 1 μg/kg/h in the first hour, and then it was continued by decreasing the dose to 0.5μg/kg/h during the surgery until tracheal resection. Group C patients received Nacl 0.9% infusion over a similar period of time, and a similar volume such as group D. Maintenance of anesthesia was performed using isoflurane (end-tidal 0.5-1.6%), infusion of fentanyl 2 μg/kg/h and rocuronium 0.1 mg/kg/h. During *cardiopulmonary bypass* (CPB), the pump flow was maintained at 2.5-3 L / min, and hematocrit levels were between 25% and 30%. Sodium nitroprusside infusion in a dose of 1.6 μg/kg/min during CPB was performed to maintain a mean arterial pressure of 30 to 70 mm. Inotropic support during CPB with epinephrine (0.02-0.1 μg/kg/min) and milrinone (0.5-1.2 μ g/kg/min) was used to facilitate the weaning from the CPB. Right after sternotomy and direct exposure to the pulmonary artery, the artery catheter was entered into the main pulmonary artery by the surgeon. Then pulmonary arterial systolic pressure (PASP) and the ratio between PASP and SSBP was calculated and recorded in three phases: 1) immediately after sternotomy, 2) after removing the aortic clamp and 3) 10 minutes after the start of protamine infusion.

In the ICU-OH unit, the infusion of the study drug continued until extubation. The sedation level of the patients was evaluated every 1 hour by the Ramsay sedation scale. To maintain the Ramsay scale between 3 and 5, infusions of morphine 0.05 mg/kg and midazolam 0.3 mg/kg were used as needed. Immediately after admitting the patient in the ICU-OH, and every 12 to 24 hours after the CPB, the PASP / SSBP of the patient was evaluated by esophageal echocardiography. The duration of mechanical ventilation, the duration of hospitalization in ICU-OH, and the need for inotropic support were recorded for all patients during the first 24 hours. The calculation of the sample size was calculated based on the primary purpose of the study, and the ratio between PASP and SSBP.

A sample group of 33 was suggested in each group by a statistician. The test statistic used is the two-sided Z test with pooled variance. $P<0.05$ was meaningful in this study.

Results

Sixty-six patients were enrolled in two groups of 33. No patient was excluded from the study groups Table 1 shows no statistically significant difference between baseline demographic information and surgical information between the two groups; thus, the two groups are statistically comparable.

Table1. Demographic Characteristics of Participants

Characteristics	Group D (n=33)	Group C (n=33)	*P*
Age (month)	7.19	7.27	0.88
Sex (male/female)(n)	7(21.2%)/26(78.8%)	14(42.4%)/19(57.6%)	0.64
Weight(kg)	5.90	6.37	0.156

The calculated PASP and PASP/SSBP ratios were lower in the dexmedetomidine group than the control group; this reduction was statistically significant (P<0.001). In addition, the percent decrease in the PASP was significantly higher than the SSBP. Although the SSBP level was slightly lower in the dexmedetomidine group, it remained statistically unchanged during the surgical period (P>0.001) (Table 2).

Table 2. Pulmonary artery systolic pressure, systemic systolic blood pressure, and the ratio between them throughout surgery

	Group D	Group C	*P*
PASP after sternotomy (mmHg)	25.3±2.23	44.29±3.05	<0.001*
SSBP after sternotomy (mmHg)	100.9±12.46	107.8±17.2	0.28
PASB/SSBP after sternotomy (%)	25.07	41.08	<0.001*
PASB after aortic clamp removal (mmHg)	28±4.51	46.18±4.21	<0.001*
SSBP after aortic clamp removal (mmHg)	91.87±11.1	101.2±0.49	0.055
PASB/SSBP after aortic clamp removal (%)	30.47	45.63	<0.001*
PASP after protamine infusion (mmHg)	23.25±3.28	53.8±4.88	<0.001*
SSBP after protamine infusion (mmHg)	78.03±8.06	100.07±14.37	<0.001*
PASP/SSBP after protamine infusion (%)	29.79	53.76	<0.001*

Data are represented as mean±SD or percentage ratio. PASP, pulmonary artery systolic pressure; SSBP, systemic systolic blood pressure. *P<0.001, significantly lower in group D

In the dexmedetomidine group, reduction in the PASB and PASB/SSBP ratios continued in the post-surgical period and throughout the study period (24 hours after CPB) compared with the control group. (P<0.001) (Table 3).

Table 3. Pulmonary artery systolic pressure, systemic systolic blood pressure, and the ratio between them in the first 24 h in the PACU

	Group D	Group C	*P*
PASP 0 time at PACU (mmHg)	23.6±2.68	37.96±1.91	<0.001*
SSBP 0 time at PACU (mmHg)	93.73±12.1	100.1±11.6	0.057
PASP/SSBP ratio 0 time at PACU (%)	25.17	37.92	<0.001*
PASP 12 h at PACU (mmHg)	22.96±2.62	36.79±2.21	<0.001*
SSBP 12 h at PACU (mmHg)	92.6±14.8	100.53±16.8	0.056
PASP/SSBP ratio 12 h at PACU (%)	24.79	36.59	<0.001*
PASP 24 h at PACU (mmHg)	24.2±2.74	36±2.15	<0.001*
SSBP 24 h at PACU (mmHg)	96.6±14.7	101.2±10.9	0.015
PASP/SSBP ratio 24 h at PACU (%)	25.05	35.37	<0.001*

Data are presented as mean±SD or percentage ratio. PASP, pulmonary artery systolic pressure; SSBP, systemic systolic blood pressure. *P<0.001, significantly lower in group D

In the case of receiving inotropic drugs, the dexmedetomidine group patients required a significantly lower dose of milrinone and no need for sodium nitroprusside in the first 24 hours; however, there was no significant difference in the need for epinephrine between the two groups (Table 4).

Patients in the dexmedetomidine group needed lower levels of sedative and analgesic drugs, to the main Ramsay scale between 3 to 5, compared to the control group. The length of the ICU and hospital stay was the same in both groups. The time under mechanical ventilation was shorter in the dexmedetomidine group, but this difference was not statistically significant (Table 5).

Table 4. The need for inotropic and vasodilator support in the first 24 h

	Group D	Group C	*P*
Milrinone (µg/kg/min)	1.1±0.44	2.3±1.04	<0.001*
Epinephrine (µg/kg/min)	0.65±0.36	0.56±0.72	0.80
Sodium nitroprusside µg/kg/min)	0.91±0.64	1.46±0.74	<0.001*

Data are presented as mean±SD. *P<0.001, significantly lower value in group D.

Table 5. The need for postoperative sedation, duration of ventilation, and length of intensive care unit and hospital stay in all patients

	Group D	Group C	*P*
Midazolam (mg/kg)	0.63±0.9	2.91±2.38	<0.001
Morphin(mg/kg)	0.61±0.81	3.71±2.22	<0.001
Ventilation (h)	6.87±0.1	7.19±0.4	0.322
ICU stay (days)	6.33±1.1	6.26±1.11	0.93
Hospital stay (days)	12.8±0.7	12.1±1.2	0.96

Data are presented as mean±SD. *P<0.001, significantly lower values in group D

Discussion

The use of dexmedetomidine in the pediatric population has steadily increased over the past several years (5). Although the use of dexmedetomidine is not yet approved by the Food and Drug Administration in children, dexmedetomidine is used in several other clinical programs, beyond sedation and analgesia, in the patients admitted to ICU and patients undergoing mechanical ventilation. Some of these programs include arrhythmias treatment (10), sedation for invasive and non-invasive procedures, adjuvant during general anesthesia, benzodiazepines and opiate withdrawal symptoms treatment, and hemodynamic stability in the patients with coronary artery disease during surgery (11-13). Despite the growing interest, there is limited information on its effect on pulmonary arterial hypertension. In this study, the effects of dexmedetomidine on pediatric patients with PH in heart surgery with CPB were investigated. The findings of this study indicated that the use of dexmedetomidine was associated with a significant reduction in the PASP and the PASP / SSBP ratios and incidence of arrhythmias during the study. Computing this ratio allows for accurate interpretation of changes; since systemic blood pressure changes may affect PAP.

The observed decrease in the PASP and the PASP/SSBP ratios in this study are similar to the study by Snapir *et al.*, (14). In the Snapir study on healthy volunteers, the PASP and SSBP were decreased after administration of dexmedetomidine (0.5 µg/ml) by 70% and 15%, respectively. These effects may be beneficial due to afterload reduction on the patients with high systemic and pulmonary hypertension, or for the patients that the right and left ventricular functions are less than normal. However, when dexmedetomidine is used at higher doses, it is advisable to be more aware and accurate as it may produce different effects.

On the contrary, there is evidence that the use of dexmedetomidine may be associated with a moderate reduction in the PASP (13). In pediatric patients, a wide range of age-related factors has an effect on systemic and pulmonary hypertension and given that these two systems work in the series, the PASP/SSBP ratios are a useful calculation that allows for a more accurate interpretation of the variation.

We do not believe that dexmedetomidine has direct pulmonary vasodilation properties. Instead, we believed that pulmonary arterial hypertension decreased due to relaxation, analgesia, and possibly the result of the activation of 2-adrenergic receptors in the central nervous system leading to sympatholysis (15,16). Most patients undergoing cardiac surgery and CPB afterward, have a significant increase in the level of circulating catecholamines (17), which may lead to an increase in pulmonary vascular resistance and pressure. These patients may also benefit from a small number of central sympatholytics.

In a study by Snapir *et al*., (14) and also a study by Ebert *et al*., (15), injection of dexmedetomidine at high

doses (>2 ng/ml), which is significantly higher than the recommended therapeutic level (range of 0.4 ng/mL and 1.2 ng/mL) leads to a progressive increase in pulmonary and systemic vascular resistance.

In this study, a lower dose of dexmedetomidine was used. Thus none of the patients had a high PASP after the administration of dexmedetomidine. The reduction in pulmonary arterial hypertension observed in our study is consistent with the results of the study performed by Abdel-Hamid and colleagues that was done on 70 children with PAH that underwent congenital heart disease surgery (5). In his study, dexmedetomidine was used from the start of the surgery up to the time of the extubation, which in the patients who received dexmedetomidine, the PASD, and PASP/SSBP were significantly decreased.

Recently, Chrysostomou *et al*., (18,19) studied the efficacy of dexmedetomidine on reducing the incidence rate of arrhythmias during surgery; they found that dexmedetomidine reduced the hypercholinergic state after the CPB, and the patients needed smaller doses of antiarrhythmic drugs during surgery.

The effect of dexmedetomidine on the PASP can be indirectly ascribed to the reduction and elimination of the need for inotropic agents during surgery. Patients in the group receiving dexmedetomidine needed lower doses of milrinone and sodium nitroprusside during the first 24 hours after surgery.

One of the reasons for the increase in the PASP after hypoxia and hypercapnia is the lack of sedation; for this reason, all the children in this study with Ramsay sedation score should be kept at sedation levels of 3 to 5. Patients in the dexmedetomidine group, during staying in the ICU, needed lower doses of sedation and analgesia that could be justified based on the mechanism of the effect of dexmedetomidine on sedation, analgesia and anxiety states without respiratory depression (19,20).

Although none of the patients in this study had an increase in the PASP after the administration of dexmedetomidine, several factors may affect on our final results, which should be considered: 1) We did not have any direct measure of cardiac contractility, it may lose the potential cardiac output fluctuations during dexmedetomidine infusion, leading to change the PASP. The dose of milrinone was lower after dexmedetomidine injection; this decrease may be related to the low cardiac output and the lower PASP. Dexmedetomidine may reduce the *catecholaminergic* state sufficiently to reduce vascular resistance, and thus may decrease blood pressure and improve cardiac output.

However, our findings do not support a major change in cardiac output, as there is a need for unchanged inotropic for epinephrine in both groups. The PASP was evaluated using echocardiography. Although this method is well-established and acceptable for the estimation of the PASP, it may not be accurate in comparison with cardiac catheterization data. However, echocardiography remains an acceptable method for evaluating the PASP.

In this study, it was concluded that the use of dexmedetomidine in children with PH would reduce the PASP during and after surgery.

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