The role of dexmedetomidine in fast-track extubation for closed congenital heart surgery in children: a randomized double-blinded placebo-controlled trial

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Background

The definition of early extubation is not well-established; some authors extended its time to 24 h postoperatively. In our study, we tried to extubate the patients by the end of the surgery. We investigated the role of dexmedetomidine use during induction of anesthesia in the improvement of outcomes with fast-track extubation in children undergoing cardiac surgery. We assumed that the use of dexmedetomidine will help in extubating the patients at the end of operation with decreased use of inhalational anesthetic and fentanyl, thus improving oxygenation and decreasing the need for analgesia postoperatively.

Patients and methods

A study was conducted in a population of 84 pediatric patients scheduled for closed congenital heart surgery. Patients were randomly allocated to two groups: group D (42 patients), which received a single dose of dexmedetomidine 0.4 mg/kg over 10 min in the induction of anesthesia, and group C (42 patients), which received normal saline. Both groups were compared in relation to percentage of extubated patients by the end of the surgery as primary outcome. Hemodynamics (mean arterial blood pressure and heart rate), sevoflurane consumption, fentanyl consumption, incidence of postoperative infection, and length of ICU stay were recorded. Arterial blood gases were analyzed before extubation and in the ICU 1 and 3 h after transfer to the ICU.

Results

Compared with the control group, group D showed lower intraoperative sevoflurane and fentanyl consumption (14.2±2.9 vs. 37.8±24.1, $P<0.01$; 48±12.5 vs. 85.2±43.2, $P<0.01$). The blood pressure at T1 and T2 showed a statistically significant decrease compared with baseline ($P=0.05$ and 0.01, respectively) and heart rate showed a significant decrease ($P=0.05$) at T1 and ($P<0.01$) at T2. Group D showed a higher incidence of successful extubation (64 vs. 26.7%, $P=0.04$) and higher pO_2 after extubation (82±28.45 vs. 68±0.23, $P=0.04$). The length of ICU stay was lower in group D (1.8±0.8) compared with 5.5±3.2 in the control group ($P<0.01$), and the incidence of postoperative infections was lower in group D compared with group C (29.4 vs. 65.2%, $P=0.04$).

Conclusion

Adding dexmedetomidine as an adjuvant to induction of anesthesia in children undergoing congenital heart surgery improved the success of extubation, the oxygenation, and decreased the length of hospital stay.

Keywords:
congenital heart surgery, dexmedetomidine, early extubation

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Introduction

Advantages of early extubation include avoidance of airway irritation, edema, accidental extubation, pulmonary hypertensive crisis during suction from endotracheal tube, chest infection, and pneumothorax related to prolonged ventilation; other advantages include early mobilization of the patient, early ICU discharge, and reduced costs [1].

Surgery for congenital cardiac disease always required mechanical ventilation that is continued postoperatively in the ICU (which may extend to days). Early extubation in the operating room (OR) was attempted in our study immediately in the OR after surgery. The definition of early extubation is not well-established; some authors extended its time to 24 h postoperatively [2].

Many anesthetic techniques can be used for fast-track extubation in pediatric cardiac patients, such as the use of a large dose of opioids, neuroaxial technique, and nonopioid analgesia. The use of a short-acting α2 agonist dexmedetomidine as an induction agent can help in extubating the patients at the end of operation by decreasing the use of inhalational anesthetics and narcotic use as well as improving oxygenation, thus helping extubation in OR and avoiding the unnecessary delay in the discharge from the ICU.

Patients were considered for extubation at the end of surgery if they were hemodynamically stable and having satisfactory arterial blood gases (ABGs).

Aim of the work

The aim of this study was to evaluate the effect of dexmedetomidine as an adjuvant drug during the induction of anesthesia on the fast-track technique in closed pediatric cardiac surgery.

Patients and methods

This randomized controlled double-blinded study was conducted in Cairo University Hospitals after obtaining the ethical committee approval. Written informed consent was obtained from the guardians of the children. Randomization was carried out using a computer-generated sequence, and concealment was carried out using opaque envelopes. This study was conducted from December 2014 to May 2015 (18 months). Patients were randomly allocated to two equal groups of 42 patients each. Pediatric patients with congenital heart diseases (otherwise healthy) who were older than 2 months and weighed more than 6 kg and scheduled to undergo closed heart surgery were included in the study. Patients requiring preoperative mechanical ventilation or high inotropic support (>0.1 mcg/kg/h adrenaline and 15 mcg/kg/h dobutamine) or those sensitive to any of the drugs used in the study were excluded from the study.

Patients were allocated on the morning of surgery to two groups: group D (42 patients), which received dexmedetomidine 0.4 mcg/kg administered over 10 min during the induction of anesthesia, and group C (42 patients), which received saline. All operations were performed by one surgeon.

The anesthesiologist interviewed the guardians and examined the patients. All patients were subjected to routine investigations, which included complete blood count, coagulation profile, liver function tests, renal function tests, blood grouping, chest radiography, recent echocardiography, and angiography if available.

Anesthetic technique

Children in both groups received midazolam 0.3 mg/kg intramuscularly and atropine 0.02 mg/kg intramuscularly 10 min as premedication induction.

Induction of anesthesia in both groups was carried out using sevoflurane and fentanyl 1–5 μg/kg. Atracurium 0.5 mg/kg was administered to facilitate endotracheal intubation and repeated intraoperatively as required to maintain muscle relaxation. Anesthesia was maintained using sevoflurane 0.3–1.5% in oxygen–air mixture (1 : 1 ratio to keep end-tidal CO_2 between 30 and 35). Dexmedetomidine 0.4 mg/kg diluted with normal saline in 10 ml was administered over 10 min in group D (the dexmedetomidine group). Group C (the control group) was administered 10 ml of normal saline during induction to assure double-blinded study. A central venous line was inserted and an arterial line for invasive blood pressure monitoring. The incremental doses of fentanyl were given if needed at a dose of 1–2 mcg/kg, and atracurium infusion was carried out at a rate of 0.5 mg/kg/h to maintain muscle relaxation. The use of inotropes was guided by the patient's hemodynamics after surgical repair.

At the end of the operation, ABG was analyzed and accordingly the effects were reversed with the intravenous administration of atropine, 0.01 mg/kg, and neostigmine, 0.05 mg/kg, or remained ventilated. Ketorolac suppository 50 mg/kg was administered for postoperative analgesia. Patients were extubated when conscious, breathing with adequate tidal volume and adequate oxygenation (75–80% in cyanotic patients and 95% in acyanotic patients at FiO_2 0.3), and hemodynamically stable. The patient was transferred to the surgical ICU adjacent to the OR.

Both groups were compared in relation to percentage of extubated patients by the end of the surgery as primary outcome. Mean arterial blood pressure and heart rate were measured at baseline, 10 min after induction (T1), and 1 h after induction (T2). Sevoflurane consumption was calculated at the end of operation with Maquet anesthesia machine using fixed fresh gas flow of 1 l. Fentanyl consumption, incidence of postoperative infection, and ICU stay were also recorded.

ABGs (pH, pO_2, and CO_2) were analyzed before extubation and in the ICU 1 and 3 h after transfer to the ICU.

Statistical analysis

SPSS (SPSS IBM company USA, Chicago) (version 15) and Microsoft Excel 2016 were used for analysis.

Categorical data were presented as frequency (%) and analyzed using the χ^2-test. Continuous data were presented as mean and SDs and analyzed using the unpaired *t*-test and the Mann–Whitney test as appropriate. Repeated measures were analyzed using the analysis of variance test for repeated measures.

A *P* value less than or equal to 0.05 was considered statistically significant and *P* value less than or equal to 0.01 was considered highly significant.

Sample size

The primary outcome in our study was the incidence of successful extubation. We calculated the sample size using Medcalc software to detect a difference of 35% between the two study groups. Having a study power of 80% and an α error of 0.05, a minimum number of 36 patients was needed for each group. We increased the number by 20% to be 42 patients per group to compensate for possible dropouts [3].

Results

Demographic data

Among 84 patients included in the study, no significant differences were reported in demographic data or type of surgery (Table 1).

Hemodynamic data

The mean arterial blood pressure at T1 and T2 showed a statistically significant decrease compared with baseline (P<0.01 and 0.01, respectively) and heart rate showed a significant decrease (P=0.05) at T1 and a highly significant decrease at T2 (P<0.01) in the dexmedetomidine group (Table 2 and Figs 1 and 2).

Table 1 Demographic data and type of operations

	Group D (dexmedetomidine) (*n*=42) [*n* (%)]	Group C (control) (*n*=42) [*n* (%)]	*P* value
Sex			
Male	23 (54)	19 (46)	0.5
Female	18 (46)	24 (54)	0.5
Age (years)	1.1±0.94	1.7±0.97	0.3
Weight (kg)	8.4±3.6	10.1±3.1	0.4
Type of operation			
BT shunt	5 (11.9)	7 (16.6)	
Fontan	8 (19)	5 (11.9)	
Glenn	9 (21.4)	8 (19)	
Coarctectomy	8 (19)	8 (19)	
PDA closure	7 (16.6)	6 (14.2)	
PAB	5 (11.9)	8 (19)	

BT, Blalock–Taussig; PAB, pulmonary arterial banding; PDA, patent ductus arteriosus.

Extubation data (arterial blood gases and percent of extubation)

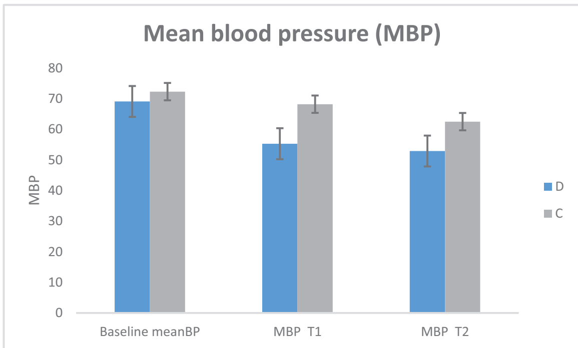
In this study, the pH before extubation in the control group showed a significant decrease, with a mean of 7.33±0.046 compared with 7.35±0.069 in the study group (P=0.05). There was a highly significant decrease 1 and 3 h after extubation in the study group compared with the control group (P=0.01) (Table 3 and Figs 3, 4 and 5).

pCO_2 showed a significant decrease 1 h after extubation in group D compared with group C (39±5.4 vs. 46±7.04, P=0.02). pO_2 showed a significant increase in

Table 2 Difference between two groups in mean heart rate and mean blood pressure at baseline, T1, T2

	Group D (n=42)	Group C (n=42)	*P* value
Baseline heart rate	130.3	136.7	0.5
Heart rate at T1	120.5	140.2	0.05*
Heart rate at T2	109.7	128.7	<0.01†
Baseline mean blood pressure	69.1	72.3	0.6
Mean blood pressure at T1	55.3	68.2	<0.01†
Mean blood pressure at T2	52.9	62.5	0.01†

Figure 1



Significant decrease of mean arterial blood pressure at T1 (p=0.05), and highly significant decrease at T2 (p<0.01) in dexmedetomidine group.

Figure 2

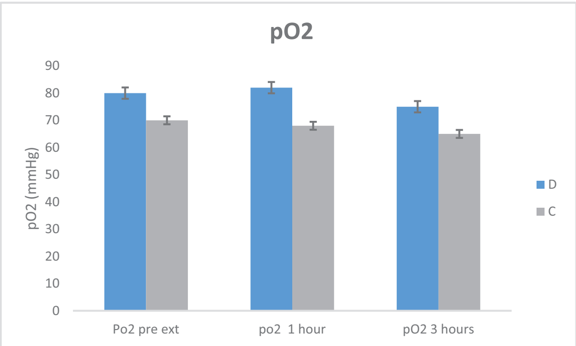
Significant decrease of heart rate at T1 (p=0.05) and highly significant decrease at T2 (p<0.01) in dexmedetomidine group.

Table 3 Differences in pH, pO2, pCO2 and percentage of extubated patients in both groups

	Group D (n=42)	Group C (n=42)	*P*-value
pH (pre-extubation)	7.35±0.069	7.33±0.46	0.05*
pH (one hour after extubation)	7.41±0.015	7.35±0.032	0.01†
pH (3 hours post extubation)	7.42±0.037	7.38±0.021	0.01†
pO2 (prextubation)	80±3.75	70±0.13	0.05*
pO2 (one hour after extubation)	82±28.45	68±0.23	0.04*
pO2 (3 hours post extubation)	75±18.32	65±0.33	0.06
pCO2 (pre-extubation)	40_±6.7	42±5.4	0.21
pCO2 (one hour after extubation)	39±5.4	46±7.04	0.02*
pCO2 (3 hours post extubation)	40±6.7	45±8.21	0.15
Percentage of extubated patients	64%	26.7%	0.04*

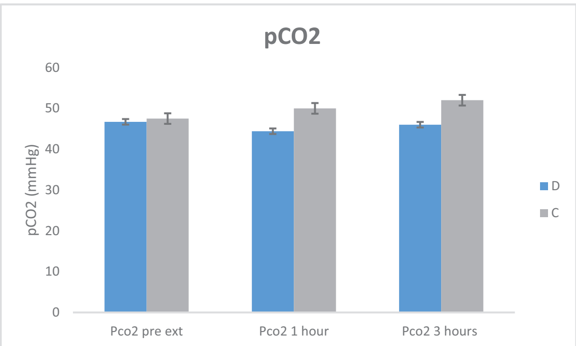
*= significant ,†= highly significant.

Figure 3



Significant increase at pre-extubation time and one hour post extubation (p=0.05),(p=0.04)in dexmedetomidine group.

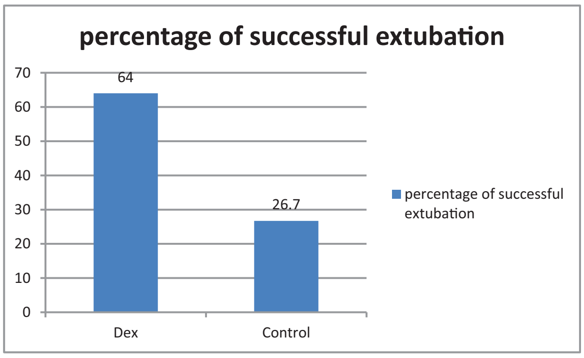
Figure 4



Significant decrease of pCO2 in dexmedetomidine group one hour post extubation (p=0.02).

the dexmedetomidine group compared with the control group both before extubation (80±3.75 vs. 70±0.13, P=0.05) and 1 h after extubation (82±28.45 vs. 68 ±0.23, P=0.04). pCO_2 change was not statistically significant even after 3 h of extubation.

Figure 5



Percentage of successful extubation in Dex group compared to control group.

Table 4 Difference in fentanyl and sevoflurane consumption between both groups

	D group (n=42)	C group (n=42)	*P* value
Mean fentanyl consumption in µg	48±12.5	85.2±43.2	<0.01†
Mean sevoflurane consumption in ml	14.2±2.9	37.8±24.1	<0.01†

†= highly significant.

The percentage of successful extubation was 64% in the dexmedetomidine group compared with 26.7% in the control group, with a significance of 0.04.

Intraoperative fentanyl and sevoflurane consumption

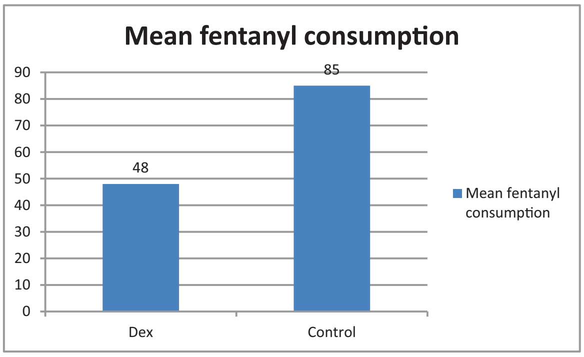
The mean consumption of fentanyl in the dexmedetomidine group was 48±12.5 µg/kg compared with 85.2±43.2 µg/kg in the control group (P<0.01). The mean consumption of sevoflurane in the dexmedetomidine group was 14.2±2.9 ml compared with 37.8±24.1 ml in the control group (P<0.01) (Table 4 and Figs 6 and 7).

Postoperative data

Ketorolac was used for postoperative analgesia. Time to first postoperative dose was recorded in both groups. The time to first dose in the dexmedetomidine group was after 5.5±1.67 h and after 3.2±1.09 h in the control group with a significant difference (P=0.05) (Table 5 and Figs 8 and 9).

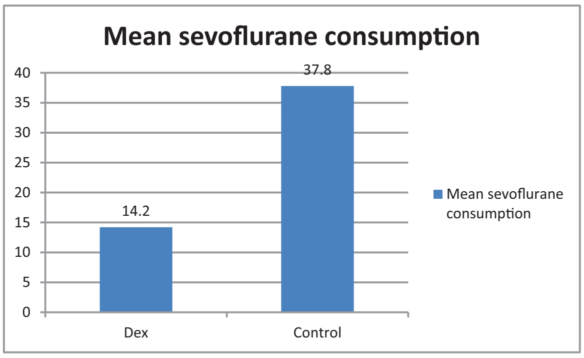
The percentage of postoperative infections in the dexmedetomidine group was 29.4% compared with 65.2% in the control group (P=0.04). The mean ICU stay was shorter in the dexmedetomidine group (1.8±0.8) compared with that in the control group (5.5±3.2) (P<0.01).

Figure 6



Comparison between mean fentanyl consumption in μg in both groups.

Figure 7



Comparison between the mean consumption of Sevoflurane in ml in both groups.

Table 5 Difference between time needed for first dose ketorolac, incidence of post operative infections and mean ICU stay

	Group D (n=42)	Group C (n=42)	*P* value
Time needed for first dose ketorolac	5.5±1.67	3.2±1.09	0.05*
Incidence of postoperative infections	29.4%	65.2%	0.04*
Mean ICU stay (days)	1.8±0.8	5.5±3.2	<0.01†

*=significant , †=highly significant.

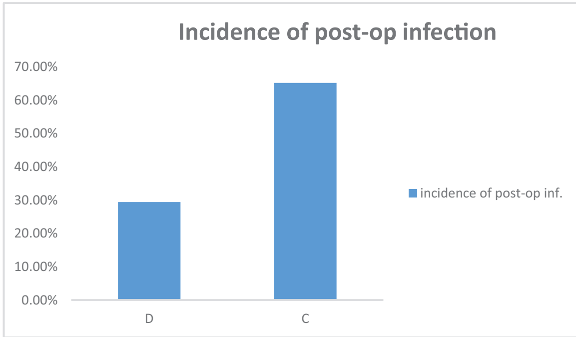
Mortality occurred in two cases in the control group compared with one case in the dexmedetomidine group and was due to postoperative infection and sepsis.

Discussion

Dexmedetomidine improved the success of fast-track extubation in pediatric patients undergoing closed cardiac surgery. The percentage of successful extubation was 64% in the dexmedetomidine group compared with 26.7% in the control group, with a significance of 0.04.

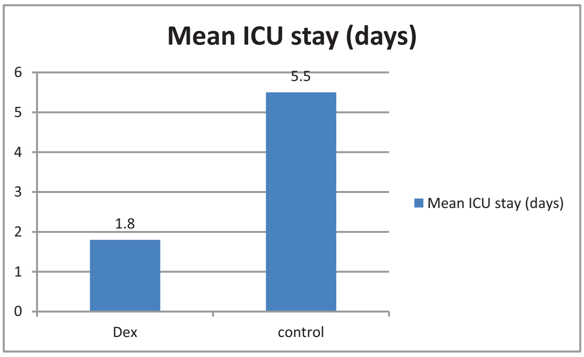
Our attempt to facilitate early extubation using a single dose of dexmedetomidine decreased the doses

Figure 8



Incidence of postoperative infections (29.4% in compared to 65.2 % in control group with p value 0.04).

Figure 9



Difference in ICU stay in both groups.

of intraoperative inhalational anesthetic and narcotics, as the mean consumption of sevoflurane in the dexmedetomidine group was 14.2±2.9 ml compared with 37.8±24.1 ml in the control group ($P<0.01$) and the mean consumption of fentanyl in the dexmedetomidine group was 48±12.5 μg/kg compared with 85.2±43.2 μg/kg in the control group ($P<0.01$).

Dexmedetomidine is a potent, highly selective, and specific α2-adrenoreceptor agonist, which lowers blood pressure and heart rate. It can be used as a sedative, analgesic, anxiolytic, and an adjuvant to general anesthesia [4,5].

Extubation inside the OR in pediatric congenital heart surgeries in our country is not a common practice. To our knowledge, we were the first to use dexmedetomidine as a small single dose in closed heart surgery to help extubation by the end of the surgery.

Patients were extubated when they were conscious, breathing with adequate tidal volume and adequate oxygenation (75–80% in cyanotic patients and 95% in acyanotic patients at FiO_2 0.3) and hemodynamically stable, and the doses of inotropes were guided by the patient's hemodynamics after surgical repair.

We concluded that the use of a single dexmedetomidine reduces the anesthetic requirements with minimal effect on the hemodynamics due to central and peripheral mechanisms by reduction in sympathetic tone and reduction in circulating catecholamines affecting mean arterial blood pressure and heart rate [6]. In the case of a single minimal dose use less than 1 mcg/kg, the initial transient increase in blood pressure response can be attenuated with slow infusion over 10 min, thus decreasing the incidence of complications such as hypotension, which if happened can be treated with vasopressor and fluids. Bradycardia which is more common and more serious as cardiac output is more dependable on heart rate in pediatrics, can be treated by atropine.

In addition to its analgesic effect, which is attributed to the activation of α2 adrenoreceptors in the spinal cord, it lowers the transmission of nociceptive and inhibits the release of substance p from the dorsal horn [5]. Its sedative effect intraoperatively helps in minimizing the anesthetic requirement and narcotics as well. All these can help in a smooth emergence and easy extubation guided by satisfactory ABGs on FiO_2 (0.3) as in our study.

The single early dose use of the dexmedetomidine in our study can minimize its postoperative sedation effect (compared with dexmedetomidine infusion), having no respiratory depressive effect. This was proved by one of the important detectors, which is satisfactory postoperative blood gases. The post-extubation blood gases were measured 1 h after extubation. There was a significant increase in pO_2 in the dexmedetomidine group 1 h after extubation compared with the control group (P=0.04) and a decrease in pCO_2 in the dexmedetomidine group 1 h after extubation (P=0.17) [7].

One of the famous factors that was known to affect the ventilation in pediatrics was the opioid-based anesthesia [7]. Thus, we believed that the initial single small dose of dexmedetomidine 0.4 mg/kg/min lowered the intraoperative fentanyl requirements, thus making early extubation easier, especially in low-weight patients, as dexmedetomidine had an analgesic effect as well as prolonged duration of postoperative need for analgesia. Time to first ketorolac dose was 5.5±1.67 h in the dexmedetomidine group compared with 3.2±1.09 h in the control group, with a significant difference (P=0.05).

An interesting finding in our study is that early extubation decreased the risk for postoperative infection in the ICU, which is mostly due to the absence of ventilator-acquired chest infections in this group. This decreases the ICU stay, which is the goal of early extubation. This in turn decreases hospital stay, thus decreasing the cost. Other potential advantages of early extubation include fewer airway complications such as (a) tracheal stenosis, ventilator-associated complications, (b) parent's reduced stress, (c) reduced amount of sedatives and associated hemodynamic compromise, (d) more rapid patient mobilization, and (e) reduced costs [8].

The pathology of the patient did not affect the success of extubation. Even the patients with single ventricle pathology, such as those undergoing Glenn or Fontan procedures, were good candidates for extubation. A study of 50 patients undergoing bidirectional Glenn or Fontan procedures who were early extubated showed improved hemodynamics (improved pulmonary artery pressure and increased cardiac index) compared with pre-extubation values [9].

Costs play an important role in conducting this study. In a hospital with very high flow of patients and limited resources, decreasing ICU stay significantly and consequently reducing the hospital stay for a category of cardiac surgery patients is highly beneficial. In 1980, Barash *et al.* [10] published their own experience with early extubation in 197 patients less than 3 years of age including neonates; 61% were successfully extubated in OR. The authors mentioned that any technique that allows maximal use of resources without jeopardizing patient safety is welcome. This statement seems even more appropriate at present, with cost issues being a greater concern today than 30 years ago [11].

Control of postoperative pain was achieved with ketorolac, which is reported to relieve postoperative pain in cardiac surgery despite risk for bleeding [12]. This point was important in extubated patients to avoid the use of high doses of opioids, which may compromise ventilation postoperatively. However, other researchers have adopted the use of regional anesthesia such as caudal epidural morphine 50–75 μg/kg to diminish postoperative pain [13].

An additive effect of dexmedetomidine is the analgesic effect, which increased the time needed for the first dose of ketorolac postoperatively compared with the control group.

In agreement with our study, Shruthi *et al*. [14] showed that the use of 0.5 mcg/kg of dexmedetomidine in general surgery at intubation before skin incision can attenuate the hemodynamic changes at extubation without the sedative effect of dexmedetomidine, thus making the postoperative extubation very smooth.

In contrast to our study, the study by Guler *et al.* [15] on emergence agitation stated that time to extubation and emergence were prolonged significantly, due to a higher dose of dexmedetomidine used.

A study by Hall *et al*. demonstrated that dexmedetomidine decreased minimum alveolar concentration of halothane by 90% in rats [5] due to its greater specificity to $\alpha 2$ adrenoceptors and its analgesic effect compared with clonidine, which decreased minimum alveolar concentration by 48% [4,5].

Settings in surgery for congenital heart diseases in which fast-tracking cannot be considered safe include all patients who are hemodynamically unstable, coagulopathic patients, or patients who do not meet generally accepted extubation criteria detected with pre-extubation ABGs [16].

Another study by Lawrence *et al.* [17] demonstrated that Hospital and ICU costs for patients who were extubated in the OR at the end of the procedure were 31 and 35% lower, respectively, compared with costs for children who were extubated later in the ICU. There was no difference in early morbidity or in survival rates with a follow-up of more than 12 months. However, in our study there was a marked reduction in infections in the ICU, which goes side by side with the absence of postoperative ventilation in the early extubation group.

Our study was limited to patients undergoing closed heart surgery. We recommend that future studies be conducted on patients undergoing open heart surgery.

Conclusion

Early extubation for congenital cardiac surgery is an old concern. However, safety of the patients was the main obstacle for achieving it. Adding a single small dose of dexmedetomidine as an induction agent helps to achieve a better outcome with pain relief and better respiratory function both intraoperatively and postoperatively without detected complications.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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