Dexmedetomidine-ketamine sedation among pediatric patients with Fallot tetralogy undergoing cardiac multislice spiral computed tomography

Hoda Shokri[a], Amr A. Kasem[a], Ihab Ali[b]

Departments of [a]Anesthesiology, [b]Cardiothoracic Surgery, Ain Shams University, Cairo, Egypt

Correspondence to Hoda Shokri, MD, PhD, Department of Anesthesiology, Ain Shams University, Cairo, 11772, Egypt.
Tel: +20 121 117 9234; fax: (+202)26845174; e-mail: drhoda10@yahoo.com

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Background
The combination of dexmedetomidine and ketamine is feasible for pediatric procedural sedation, particularly in radiologic imaging studies.
Objective
The aim of the study was to investigate the sedative effects of ketamine-dexmedetomidine (KD) and ketamine-midazolam (KM) combinations on recovery time and adverse events in pediatric patients with uncorrected tetralogy of Fallot undergoing multislice spiral computed tomography (CT).
Patients and methods
A total of 40 American Association of Anesthesiologists III pediatric patients aged between 2 and 3 years with surgically uncorrected tetralogy of Fallot undergoing CT were randomly allocated into two equal groups. Patients in group KD received intravenous dexmedetomidine (1 μg/kg) over 15 min, followed by 1 mg/kg of ketamine infused slowly over 15 min. Patients in the group KM received 0.1 mg/kg bolus of midazolam over 15 min, followed by 1 mg/kg initial bolus of ketamine over 15 min, followed by waiting for 2 min to evaluate the sedative effect. After a Ramsay sedation score of 4 was reached, a rescue dose of 1 mg/kg of ketamine (maximum of 2 mg/kg) was administered to maintain an Ramsay sedation score of 4 in both groups. Recovery time; sedation scores, systolic blood pressure and diastolic blood pressure, and oxygen saturation at baseline, 3, 6, and 9 min after drug administration; the number of patients requiring additional ketamine; and the incidence of complications such as apnea, hypotension, and vomiting were recorded.
Results
Administration of KM compared with KD was associated with significantly larger number of patients requiring additional ketamine doses (P=0.018) and a higher incidence of complications, such as tachyarrhythmia (P<0.035), vomiting (P<0.02), and agitation (P<0.04) as well. There was no significant difference between both groups regarding recovery time, sedation scores, systolic blood pressure, diastolic blood pressure, and oxygen saturation.
Conclusion
Sedation using KD for cardiac multislice spiral CT displayed lower rescue doses of ketamine and less occurrence of complications with insignificant effect on the recovery time compared with KM sedation.

Keywords:
dexmedetomidine, ketamine, midazolam, pediatric, spiral computed tomography, tetralogy of Fallot

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Introduction

Tetralogy of Fallot (TOF) represents 10% of all congenital heart diseases (CHDs) [1]. It results in intra-cardiac right-to-left shunting. TOF is associated with the presence of a ventricular septal defect, pulmonary outflow obstruction, an overriding aorta, and right ventricular hypertrophy [1].

Cardiac imaging plays a vital role in the surveillance of patients with TOF by measuring anatomic and functional abnormalities, diagnosing extracardiac structural anomalies, and showing the development of the pulmonary artery. Furthermore, it assists clinicians in clinical decision making and risk stratification [2].

In pediatric patients with TOF, blood oxygenation depends on the severity of the anatomic defects. It typically ranges from 60 to 90%. It varies from

asymptomatic or mild cyanosis to profound cyanosis at the time of birth. Cases in which cyanosis is absent are referred to as pink tet [3].

TOF is associated with hypercyanotic spells, which are characterized by cyanosis, shortness of breath, and loss of consciousness. Accordingly, it may be caused by pain, dehydration, or fever resulting in decreased oxygen saturation, which, in turn, increases pulmonary vascular resistance with increased right-to-left intracardiac shunting across the ventricular septal defect [4].

Management of children with CHD has been considered a great challenge for anesthesiologists. General anesthesia with positive pressure ventilation can alter the intracardiac pressures as well as the shunt fraction. Therefore, deep sedation with a pain-free, spontaneously breathing patient is preferred by the anesthetist [3].

Dexmedetomidine (DEX) is a selective α-2-adrenergic agonist that is under investigation for its potential in anesthesia because of its combined sedative, hypnotic, and anxiolytic effects [4]. The application of DEX is encouraged in patients with a right-to-left shunt, especially in TOF [5] because it attenuates the increase in both mean blood pressure and mean pulmonary artery pressure in patients with pulmonary hypertension undergoing mitral valve replacement surgery [6,7].

A previous study suggested DEX represents an attractive sedative option in patients with TOF, particularly small infants, owing to its shorter recovery period, its sympatholytic effect, minimal effect on respiration, and maintenance of the systemic vascular and venous resistance, in addition to decreasing oxygen consumption [8].

The beneficial effects of ketamine have been attributed to its *N*-methyl-d-aspartate receptor antagonism [9]. Ketamine is used as an adjuvant because it is an opioid receptor agonist, in addition to its interaction with voltage-gated sodium channels [10,11]. The main advantage of ketamine is its potency as both a sedative and analgesic while increasing the heart rate, which maintains the rate-dependent cardiac output in pediatric patients [12].

Interestingly, the sympathoinhibitory effects of DEX are balanced with the cardio-stimulatory effects of ketamine, thus maintaining a stable hemodynamic profile within the normal physiological range [13]. Midazolam, a very short-acting benzodiazepine, is another commonly used sedative agent that also has hypnotic, anxiolytic, and anticonvulsant properties, and causes anterograde amnesia [14].

The aim of the present study was to investigate the sedative effects of ketamine-dexmedetomidine (KD) and ketamine-midazolam (KM) combinations on recovery time and incidence of adverse events in pediatric patients with uncorrected TOF undergoing multislice spiral computed tomography (MSCT).

Patients and methods

Study population

A total of 40 patients aged between 2 and 3 years were enrolled in this randomized, double-blinded parallel-group prospective study at Ain Shams University hospital between February and July 2019. All patients had an American Association of Anesthesiologists III physical status and a surgically uncorrected TOF for MSCT. Ethical approval was provided by the Local Ethics Committee (FMASU R 20/2018), and informed consent was obtained from all parents. The trial was registered under the number PACTR201906664920036. This study was carried out according to the Declaration of Helsinki. Patients with an active chest infection, renal impairment, parental refusal to participate, hypersensitivity or contraindication to the study drugs, hepatic dysfunction, patients with multiple congenital anomalies, and patients receiving digoxin were excluded.

Patient recruitment and randomization

Patients were randomly divided into two groups using a sealed envelope technique. Allocation of patients was performed according to a computer-generated randomization list, with a 1 : 1 allocation. Randomization was performed using an opaque-sealed envelope, prepared and opened by a staff member not involved in the study. Patients in the KD group (n=20) received 1 μg/kg of intravenous (i.v.) DEX over 15 min (Precedex 200 μg/2 ml; Abbott Laboratories, Abbott Park, Illinois, USA). Subsequently, 1 mg/kg of i.v. ketamine over 15 min (Ketalar, 50 mg/ml, 10 ml; Pfizer, Sandwich, UK) was administered.

Patients in the KM (n=20) received 0.1 mg/kg of i.v. midazolam over 15 min (Dormicum, 1 mg/ml, 5 ml; Deva Holding, Istanbul, Turkey), followed by a 1 mg/kg i.v. bolus infusion of ketamine administered over 15 min (Ketalar, 50 mg/ml, 10 ml; Pfizer, USA). This

combination is usually used in our institution. Following adjustment using the aforementioned technique and a waiting period of 2 min, the sedative effect was evaluated, and then the procedure was started when Ramsay sedation score (RSS) of 4. The bolus doses of the study drugs were calculated according to the patient's body weight and then they were withdrawn and completed with normal saline 0.9% in a 10-ml identical syringe. DEX concentration (1 μg/ml), ketamine concentration (2 mg/ml), and midazolam concentration (0.2 mg/ml) were achieved.

Patient responses to tactile and verbal stimuli were evaluated 2 min after ketamine administration. A rescue dose of 1 mg/kg of ketamine (maximum of 2 mg/kg) was administered over 15 min intervals in patients with an RSS less than 4. The principal investigator and nursing staff were blinded to the study grouping.

Anesthetic technique

Preoperative anesthetic check-up and cardiological consultation were performed on the evening before surgery. Preoperative investigations included complete blood count, chest radiography, and echocardiography.

Patients were required to fast for 6 h for solid food and 3 h for clear fluids before the procedure, and no premedications were given. EMLA cream was applied to the site of cannula insertion 1 h before the procedure. Subsequently, 20 ml/kg of ringer acetate was administered. Standard monitoring included ECG, blood pressure, and pulse oximetry. All patients were given 100% supplemental oxygen (3 l/min) via nasal prongs. After the procedure, patients were placed in post-anesthesia care unit under continuous monitoring by a trained resident and an experienced nurse who were unaware of the nature of the study until complete recovery. Intensive care unit beds supplemented with resuscitation equipment, monitors, and oxygen were available in the case of serious complications, up to cardiac arrest. Hemodynamic variables were recorded before administration of the study drug (baseline value), followed by every 3 min until the end of the procedure. In the event of hypotension (defined as a >20% decrease compared with baseline mean blood pressure), patients were to be primarily treated with fluid resuscitation (10 ml/kg of ringer acetate) and vasopressors, such as phenylephrine (5–20 μg/kg/dose every 20 min as required). The degree of sedation was evaluated using the RSS [15], where 1=anxious or restless; 2=cooperative, orientated, and tranquil; 3=responding to commands; 4=asleep with brisk response to stimulus; 5=asleep with sluggish to stimulus; and 6=deep sleep with no response to stimulus.

Sedation levels were assessed by an anesthesiologist at 2 min intervals for the duration of the procedure (10 min). An RSS score of 4 was expected, as the painful jet injection of the dye results in patient movement and haziness of the image, hindering the visualization of tiny vessels.

Outcome measures

The primary measure of the study was to assess the recovery time of patients, which was the elapsed time from administration of last dose of the study drug till achievement of modified Aldrete score greater than 8 (Fig. 1) [16].

Secondary measures included sedation scores, systolic blood pressure and diastolic blood pressure, and oxygen saturation at baseline, 3, 6, and 9 min after administration of the study drugs, number of patients requiring additional ketamine, as well as the incidence of adverse effects (e.g. apnea; hiccups; vomiting; hemodynamic events, such as tachyarrhythmia, bradycardia, and hypotension; and emergence reactions such as agitation). In the case of bradycardia (<5th percentile for age or 20% below baseline), 0.01 mg/kg of atropine was administered.

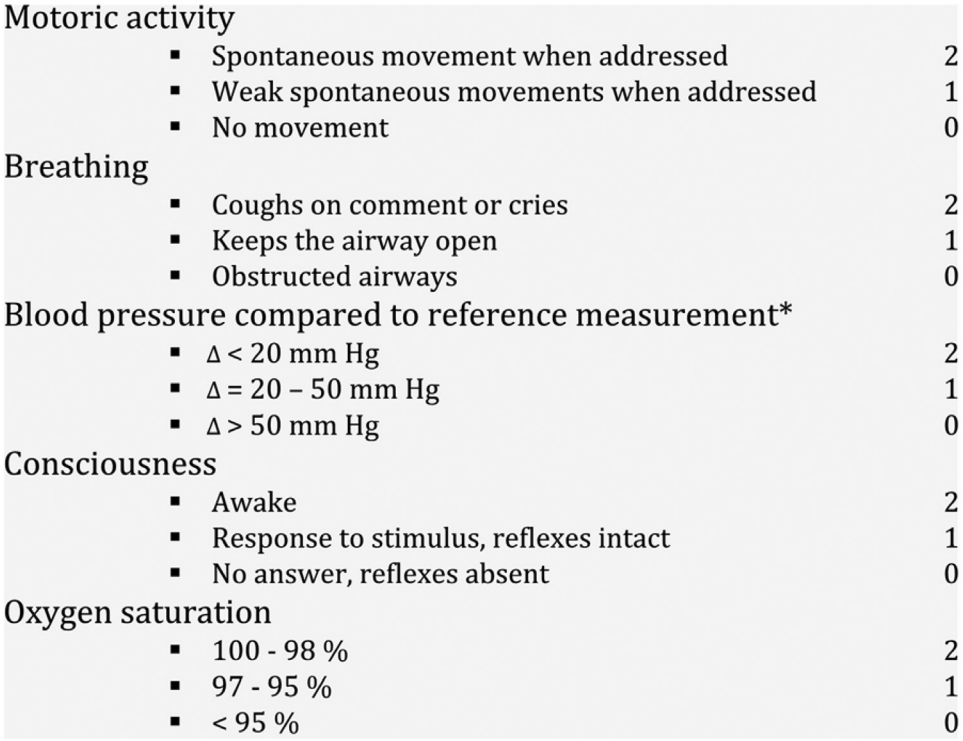
Statistical analysis

Data were analyzed using SPSS version 23 (IBM Corp., Armonk, New York, USA). Normally distributed numerical data were presented as mean and SD, and skewed data as median and interquartile range. Qualitative data were presented as number and percentage or ratio.

A previous study showed that the mean recovery time for patients administered KD was 9.3±4.5 compared with 16.2±6.5 in patients administered KM [19]. Based on this result, and in consideration of the 20% dropout rate, 20 patients were required in each group to reject the null hypothesis.

The unpaired *t*-test was applied to compare normally distributed numerical data. The Mann–Whitney test was used to compare skewed numerical data, whereas Fisher's exact test was applied for categorical data. A *P* value less than 0.05 was considered statistically significant.

Figure 1



Modified Aldrete score.

Results

A total of 40 patients were assessed for eligibility and all were enrolled in our study with no single case of protocol violation. The CONSORT flow diagram (Fig. 2) shows the progress of the patients through the various phases of the study. After randomization of the 40 patients, the trial was completed, and data were analyzed.

Demographic data and duration of surgery were comparable between the two groups (Table 1).

There was no significant difference between the study groups regarding sedation scores (Table 2).

The primary outcome was the recovery time (Aldrete score >8), and there is no significant difference between the study groups (P=0.153; Table 3).

There was a significantly higher number of patients receiving additional doses of ketamine (P=0.018), as well as a higher incidence of tachyarrhythmia (P=0.035), agitation (P=0.04), and vomiting (P=0.02) in the KM group compared with KD group (Table 3). There was no significant difference between the study groups regarding the incidence of apnea, bradycardia, and hypotension (Table 3). Hiccupping was not reported in any cases.

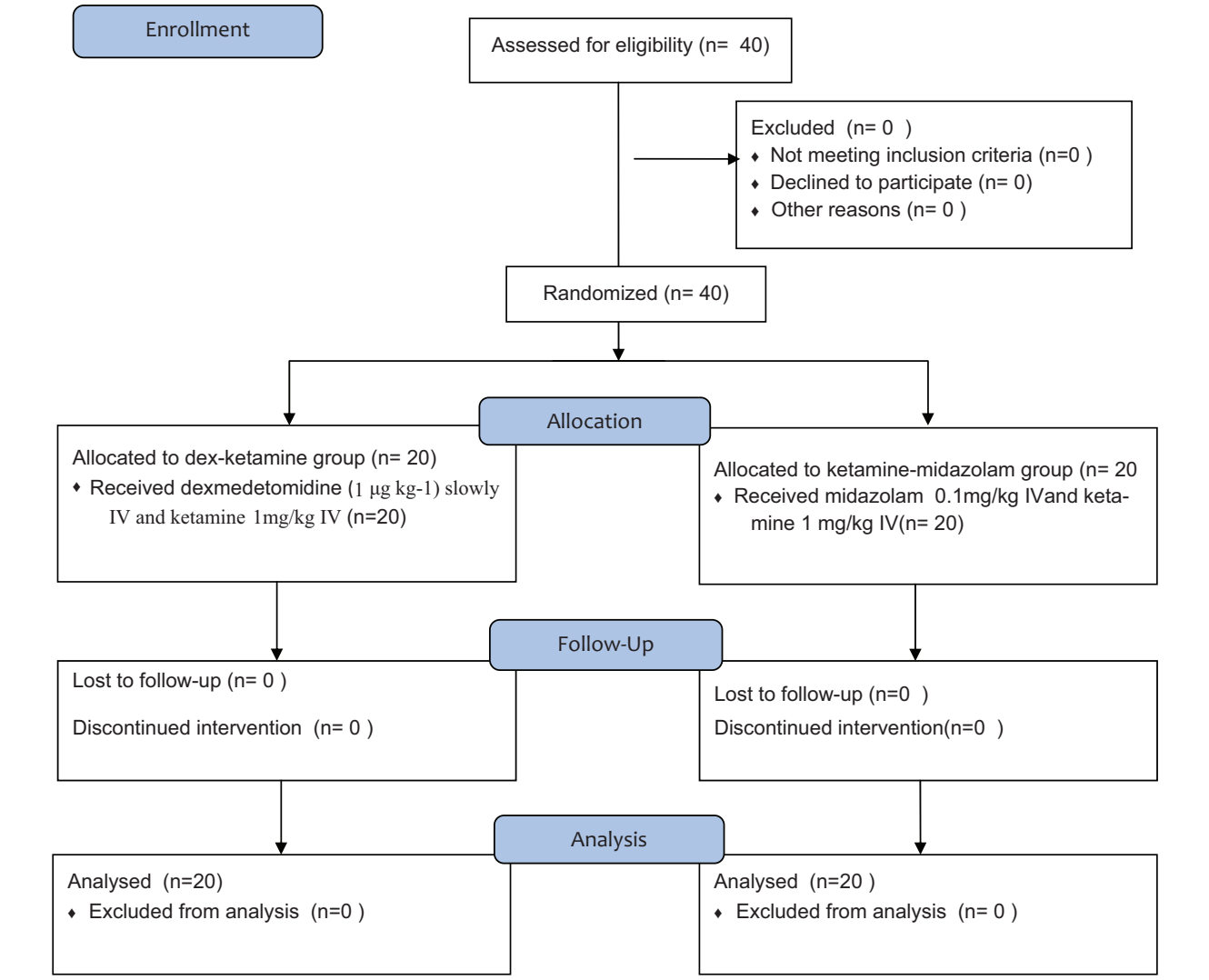
Diastolic blood pressure values were similar between KM group compared with DEX-ketamine group (Table 4). Systolic blood pressure values were comparable between KM group compared with DEX-ketamine group (Table 4).

There was no significant difference in oxygen saturation between patients in the KM and KD groups (Table 5).

Discussion

This prospective study showed that outpatient sedation using KD for cardiac MSCT displayed lower rescue doses of ketamine, as well as a lower incidence of complications, such as vomiting, tachyarrythmia, and agitation. However, the recovery time, sedation scores, and oxygen saturation values were similar between the study groups. In the study by Koruk and co-workers, procedural sedation for pediatric patients undergoing extracorporeal shock wave lithotripsy using KD was associated with a shorter recovery time compared with KM (9.3±4.5 vs 16.2±6.5 min respectively; P<0.001) and a significantly higher incidence of bradycardia (P=0.016) [17]. The results of our study are not consistent with the findings of Koruk and colleagues, which may be owing to the difference of the nature of the procedure.

Figure 2



Study flow chart.

This is consistent with a previous study performed on five patients with right-to-left shunt who underwent emergency noncardiac surgery using a KD combination. Hemodynamic variables were maintained within 10% of baseline values. There were no cases of intraoperative oxygen desaturation, hemodynamic instability, postoperative agitation, or heart failure. Furthermore, rescue doses using a vasopressor were not required to maintain systemic vascular resistance. This combination resulted in a smoother recovery [18].

Ketamine is one of the promising agents used for TOF repairing owing to its beneficial cardiovascular effects, such as increasing systemic vascular resistance, resulting in decreased right-to-left shunting. Moreover, it increases pulmonary blood flow, leading to improved oxygenation [19].

A study by Menshawi *et al.* [20], which studied the efficacy of DK compared with KM for sedation of pediatric patients undergoing cardiac catheterization, found that the administration of DK was associated with significantly shorter recovery time and lower ketamine rescue doses, with insignificant difference regarding the sedation scores, the incidence of adverse events (bradycardia), as well as the heart rate and oxygen saturation values. Our findings agree to a great extent with the results of this study.

Further comparable results to the present study were found by Kim *et al.* [21]. The administration of KD sedation in patients undergoing brain MRI revealed hypotension in only 2 of 72 patients, whereas 10 patients received additional doses of rescue sedation.

The adverse cardiovascular effects of DEX for procedural sedation have been discussed and include occasional attacks of bradycardia, with rare cases of sinus or cardiac arrest [22]. However, DEX has been reported to be effective in various cases with CHD

Table 1 Demographic and surgical data

Demographic data	KD group (*n*=20)	KM group (*n*=20)	*P* value
Sex			
Female	12 (60)	9 (45)	0.342
Male	8 (40)	11 (55)	
Age (years)	2.24±0.77	2.09±0.81	0.552
Weight (kg)	8.62±1.95	8.47±2.06	0.814
Duration (min)	9.15±1.23	8.7±1.75	0.352

Age, weight, and duration (min) are presented as mean±SD. Data on sex are presented as a percentage.

Table 2 Comparison of sedation scores between the study groups

Sedation scores	DK group (*n*=20)	KM group (*n*=20)	*P* value
2 min	4 (4–5)	4 (4–5)	0.882
4 min	4 (4–5)	4 (4–5)	0.830
6 min	4 (4–5)	3 (3–4)	0.131
8 min	4 (4–5)	4 (4–5)	0.631
10 min	4 (4–5)	3 (3–4)	0.058

Data are presented as median values.

Table 3 Comparison of adverse events, recovery time, and additional ketamine doses between the study groups

	DK group (*n*=20)	KM group (*n*=20)	Tests		Confidence interval
			t/χ^2	*P* value	
Modified Aldrete score of >8 (min)	35.25± 5.67	36.57±5.64	1.459	0.153	34.99–36.75
Additional ketamine doses	2 (10)	7 (35)	5.625	0.018*	0.011–0.891
Apnea	0	3 (15)	3.243	0.072	0.022–2.202
Hiccups	0	0	0.000	1.000	0.058–17.182
Vomiting	0	4 (20)	6.144	0.02*	0.024–0.747
Tachyarrhythmia	2 (10)	5 (25)	6.144	0.035*	0.024–0.747
Bradycardia	1 (5)	0	1.026	0.311	0.175–25.349
Hypotension	1 (5)	0	1.026	0.311	0.175–25.349
Agitation	1 (5)	3 (15)	4.329	0.04*	0.013–1.138

All data are presented as percentages with the exception of recovery time, which is presented as mean±SD. *Significant. **Very significant.

Table 4 Comparison of systolic and diastolic blood pressures between the study groups

	DK group	KM group	*P* value
Diastolic blood pressure			
Baseline value	47.55±2.24	48.60±1.85	0.114
3 min	48.85±1.53	49.0±1.59	0.762
6 min	48.95±1.23	49.20±1.47	0.563
9 min	49.50±1.19	50.0±1.59	0.267
Systolic blood pressure			
Baseline value	76.3±8.64	74.75±11.77	0.638
3 min	71.34±12.32	73.43±10.91	0.101
6 min	72.78±9.05	71.07±12.37	0.621
9 min	70.24±12.3	69.28±11.46	0.605

All data were presented as mean±SD.

Table 5 Comparison of oxygen saturation values between the study groups

	Oxygen saturation		*t*	*P* value
	DK group (*n*=20)	KM group (*n*=20)		
Baseline	87.43±2.12	87.1±2.83	0.417	0.678
3 min	82.12±1.41	81.5±2.08	1.103	0.276
6 min	83.5±2.24	84.4±1.72	1.425	0.162
9 min	85.6±2.32	86.37±2.15	1.089	0.283

All data are presented as mean±SD.

involving procedural sedation. Preliminary data revealed that the addition of ketamine to DEX has several benefits, such as maintaining the heart rate and blood pressure values within 10% of baseline values [22].

The use of i.v. KD in patients with uncorrected congenital cyanotic heart disease presenting for non-cardiac surgery has been presented previously in a case series [18]. The authors concluded that the KD combination leads to excellent hemodynamic stability in patients with cyanotic heart disease. Moreover, Mester *et al.* [23] studied the application of KD as a procedural sedation in pediatric patients with CHD. An adequate level of sedation for cardiac catheterization without significant cardiovascular or ventilatory effects was observed [23]. After review of literature by Tobias, he showed that DEX and ketamine when used together may prevent common adverse effects of ketamine such as tachycardia, salivation, hypertension, and emergence agitation; on the contrary, ketamine may prevent hypotension and bradycardia, which has been caused by DEX [13]. Additionally, ketamine speeds the onset of sedation, thus eliminating the slow onset time when DEX is used as a sole agent [24]. Despite various regimens have been introduced in the literature, the most effective regimen is the use of a bolus dose of DEX (1 μg/kg) and ketamine (1–2 mg/kg), for sedation, with supplemental doses of ketamine (0.5–1 mg/kg) as needed [13].

Limitations

This study has several limitations. The sample size was small, and adverse effects occurring at a lower

frequency could not be detected. In addition, patients were not classified as high, intermediate, or low risk. Moreover, adverse events were not divided into major or minor reactions. Another limitation is that critically ill patients were not enrolled in the study. Consequently, the application of the study findings may, therefore, be limited in clinically unstable patients with comorbidities. Further studies are required to evaluate the efficacy and adverse effects of DEX combined with other agents for procedural sedation of patients with CHDs. A future study with bigger sample size can be performed for better evaluation of the adverse events.

Conclusion

This study showed the efficacy of KD for sedation of pediatric patients with uncorrected TOF undergoing cardiac MSCT compared with KM, with the advantages of displaying lower rescue doses of ketamine and less occurrence of complications without significant effect on the recovery time. To conclude, DEX combined with ketamine is a promising alternative to KM for sedating pediatric patients with uncorrected TOF.

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Conflicts of interest

There are no conflicts of interest.

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