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Dexmedetomidine vs Ketamine for Pediatric Procedural Sedation in the Emergency Department: A Randomized Clinical Trial

Behrang Rezvani Kakhki[1], Melika Fugerdi[1], Zahra Abbasishaye[2], Hamideh Feyz Dysfani[1], Elnaz Vafadar Moradi[1*]

[1]Department of Emergency Medicine, Faculty of Medicine, Mashhad University of Medical Science, Mashhad, Iran
[2]Clinical Research Department, Development Unit, Mashhad University of Medical Sciences, Mashhad, Iran

***Corresponding author:** Elnaz Vafadar Moradi*
Address: Emergency Department, Emam Reza hospital, Razi Sq., Mashhad, Iran.
Tel: +98-51-38525312
e-mail: Vafadarme@mums.ac.ir

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ABSTRACT

Objective: To design and conduct the effectiveness of Ketamine vs Dexmedetomidine in children's sedation at emergency department (ED).
Methods: This randomized clinical trial study was carried out at the two trauma centers in Mashhad, Iran. The patients were divided into two groups by means of a random numbers table to be treated with Ketamine (N=20) or Dexmedetomidine (N=20). Their demographic information and sedation times of drugs were collected and analyzed.
Results: In general, sedation time was significantly higher in the ketamine group, 14.35 minutes (IQR:9.82-19) than in the dexmedetomidine group, 9.7 minutes (8.35-14.23) (p=0.023). Time of injection to complete anesthesia was 45.25 (IQR:30-58) and 72 (IQR:60.25-82) minutes in ketamine and dexmedetomidine groups, respectively (p<0.01). In the case of recovery, grade 4 of the Ramsey scale was statistically more prevalent in dexmedetomidine (45%) than in the ketamine group (p=0.0001).
Conclusion: This study demonstrated that dexmedetomidine could be used in cases where a shorter sedation time is vital. Ketamine could be a better choice where full recovery time (from injection) matters most.
Clinical Trial registration code: IR.MUMS.fm.REC.1396.534.

Keywords: Pediatric; Ketamine; Dexmedetomodine; Pain; Procedural.

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Introduction

Children's sedation with sedatives is of utmost significance for proper performance and success diagnosis and treatment procedures [1, 2]. Various drugs have been used for child sedation and the different diagnostic procedures' performance for years ago [3-5].

Midazolam, which is used for sedation, causes respiratory depression and in rare cases hypotension [6-8]. Propofol as an another sedative agent can cause respiratory depression and cardiovascular weakness depending on the administered dose [9-11].

Dexmedetomidine influences a selective alpha-2

receptor agonist agent in the central nervous system and result in the inhibition of norepinephrine by means of G- proteins functions [12-14].

Ketamin as a water-soluble agent of the phencyclidine family affects N-methyl-D-aspartate (NMDA) receptors which cause amnesia and central analgesia [3]. Its pharmacodynamic properties are similar to Midazolam after oral ingestion and it is used as an alternative [14, 15].

Short-term sedatives are widely used in the emergency department (ED) nowadays in order to avoid the side effects of long recovery times and prevent long-term staying and hospitalization in ED [6, 16]. In addition, children's sedation must be used for the shortest possible time and with minimum side effects and the administration must provide proper levels of consciousness and sedation and have a minimum effect on the patient's vital and hemodynamic signs [13]. Due to limited evidence on the effectiveness of ketamine and dexmedetomidine for children's sedation, this study was designed and conducted on the effectiveness of ketamine and dexmedetomidine for children's sedation in ED.

Materials and Methods

Trail Design and Participants

This is a randomized clinical trial study on traumatized children in need of laceration repair referred to the ED of Emam Reza and Hasheminejad hospitals of Mashhad in 2017.

The study was carried out at two academic trauma centers with an average entry rate of 50000 trauma patients per year, between March 21, 2017, to March 21, 2018. Children aged 2-14 years in need of sedation for laceration repair were included in the study. Patients with unstable vital signs, out-of-control hemorrhage, deep tissue (e.g. tendons, main arteries) injury, respiratory infections, allergies to commonly used drugs, psychiatric problems, and those who had already taken painkillers were excluded from the study (Figure 1).

Randomization

The research director, who was not involved in the research, enrolled the participants and divided them into two groups by means of a random numbers table. Then, a specific code was considered for each patient and it was placed inside the sealed opaque envelope based on the division of the groups. The charge nurse of administering these drugs to each patient took an envelope, while she was not aware of the conditions of the prescription, after opening the envelope, she knew the prescriptions' conditions. Blinding was performed for the researcher and health care providers and none of them were informed of the envelopes' contents.

Intervention

In the ketamine group, 1.5-2 mg/kg of medication

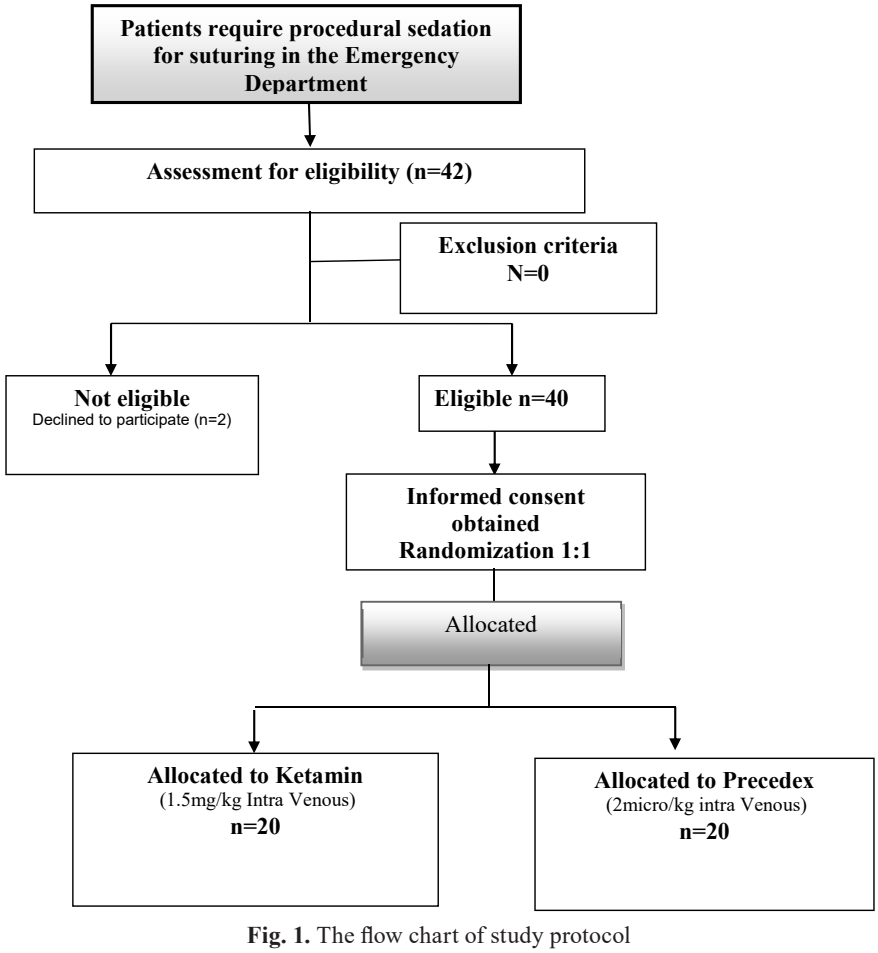

Fig. 1. The flow chart of study protocol

(Ketamine Hydrochloride Rotexmedica vial 50 mg/ml 10 ml, made in Germany) was administered intravenously (IV) followed by 1.5 ml normal saline. In the Dexmedetomidine group, 2 µg/kg of medication (Sedodex 100 mcg/ml 2ml, Imagen company, made in Iran) was administered IV as primary does, followed by 2 µg/kg after 20 minutes, as a second dose, based on the FDA recommended dose. Both drugs were diluted with 90% saline solution to a total volume of 1.5 ml. All patients received local anesthesia with lidocaine (10-60 mL of 0.5% lidocaine with a maximum dose of 200mg, Aburayhan company, made in Iran) after sedation. Patients' information including age, sex, sedative code, sedation time (interval between injection and sufficient sedation level in minutes), and patient recovery according to Ramsy Sedation Scale (RSS) (Table 1) were registered. Vital signs such as blood pressure, O2 saturation, pulse rate, respiratory rate, and RSS of the patients were measured from admission, 10 minutes after drug administration, immediately before and after treatment was assessed by a nurse using a fixed digital monitoring device. Side effects were defined as causing hypotension (blood pressure loss of more than 20% based on age), nausea, bradycardia (more than 20% loss of heat beat based on age) and tachycardia (more than 20% of heat beat rise based on age). The effects of both drugs on the patient's vital signs were also collected. Emergency medicine assistant evaluated sedation time, recovery time after sedation, attending physician's satisfaction with the procedure, and changes in vital signs or emergence side effects.

Table 1. Ramsy Sedation Score

Ramsy Sedation Score	
1	Nervous, agitated and/or restless
2	Cooperative, orientated, quite patient
3	Only obeying the orders
4	Sleeping, responding to hitting the glabella, and high voice suddenly
5	Sleeping, responding to hitting the glabella, and high voice slowly
6	No response to any of these stimulations

Sample Size

The sample size was calculated based on the clinical trials, mean comparison of two independent groups, and full recovery time using S-pooled instead of a total average standard deviations (SD) squared. Based on such assumptions and considering an alpha level of 0.05 and a study power of 90, the full recovery time was 103.25 minutes with an SD of 10.37 in the ketamine group, and 90.43 minutes with an SD of 10.32 in the dexmedetomidine group. A primary sample size of 7 patients was chosen for both groups, but taking into account a 10% rate for exclusions and after the reduction of probable errors, a sample size of 20 was finalized for each group.

Statistical Methods

We analyzed demographic and the field data of patients studied in both groups by SPSS V.20. The significance level of all tests was smaller than 0.05. The Fisher exact test was used to analyze the frequency distribution of study groups in terms of qualitative variables. The Mann-Whitney test was used to study the mean differences between study groups such as age, sedation time, and other clinical indices. In addition, the Friedman test was used to study the effects of therapy before and after the intervention.

Result

In general, 40 patients were eligible and were randomly assigned to the treatment groups (Figure 1). After allocation, none of them refused to continue treatment and all 40 participants were followed up until hospital discharge. The mean age in ketamine and dexmedetomidine groups were 6.85±2.455 and 5.15±2.834 years, respectively (p=0.056). In terms of laceration anatomic area, 12.5% (5 cases) were in the upper extremity, 5% (6 cases) were lower extremity, and 72.5% (29 cases) were in the scalp and face. Sedation time was 14.35 (IQR:9.82-19) and 9.7 (8.35-14.23) minutes in ketamine and dexmedetomidine groups, respectively (p=0.023) (Figure 2). Based on the patient's recovery and according to the Ramsey scale, grade 3 recovery was more frequent in the ketamine group (60%) compared to the dexmedetomidine group (15%). Grade 3 was 37.5%, which 80% was from the ketamine group. In addition, 9 (45%) of the participant in the dexmedetomidine group were in grade 4 on the Ramsey scale which was statistically higher than the ketamine group with 10% grade 4 participants (p=0.0001) (Table 2).

The median duration of drug effect (from the time of injection to complete anesthesia) was 45.25 (IQR:30-58) and 72 (IQR:60.25-82) minutes in Ketamine and Dexmedetomidine groups, respectively (p<0.01). The dexmedetomidine group had higher recovery times before recovery, which was statistically significant (p<0.01) (Figure 3). Physician satisfaction with patient sedation procedure based on a Likert scale

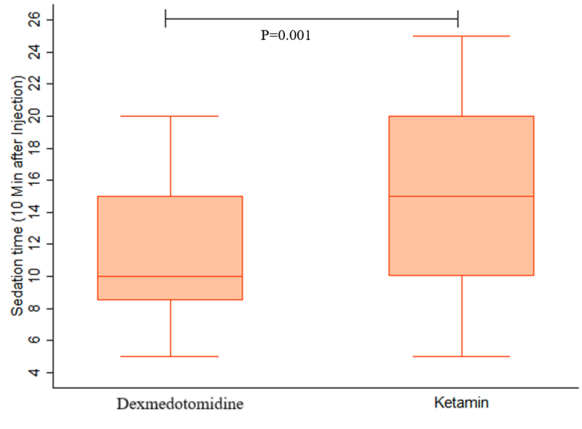

Fig. 2. Sedation time 10 minutes after drug administration in two groups.

Table 2. Patients' recovery according to Ramsy Sedation Scale (RSS)

Variables	Scale	Total frequency (percentage)	Groups		*p* value
			Ketamine	Dexmedetomidine	
RAMSY scale	2	13 (32.5%)	6 (30%)	7 (35%)	0.989
	3	15 (37.5%)	12 (60%)	3 (15%)	0.0079
	4	11 (27.5%)	2 (10%)	9 (45%)	0.0001
	5	1 (2.5%)	0 (0%)	1 (5%)	0.874

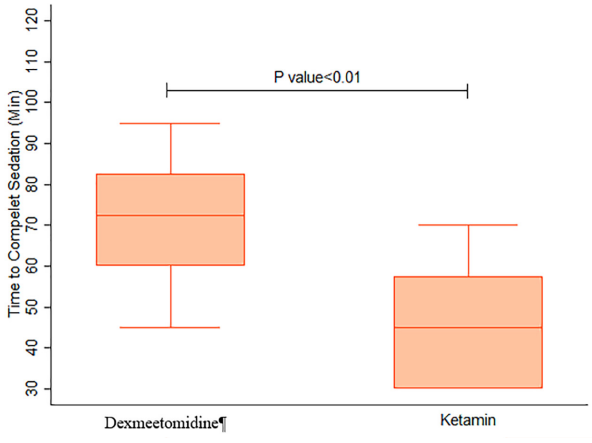

Fig. 3. Times to complete sedation in two groups.

from zero to 10, reported 87.5% full satisfaction. Physicians' satisfaction scores were 8, 9, and 10 in the ketamine group and 9 and 10 dexmedetomidine group (p=0.598). Patient's vital signs including respiratory rate (RR), O2 saturation, pulse rate (PR), and systolic blood pressure (SBP) before injection, 10 minutes after, after sedation, and before laceration repair, after repair, and at the end of procedure were evaluated separately for both groups. In both groups, those indices showed significant changes through time, therefore, all indices had decreased at the end of the procedure (p<0.05), but the range of such changes was not outside of the normal range (Table 3).

There were no adverse events reported regarding the lidocaine administration or any of the medications.

Discussion

Performance of pediatric therapy procedures in ED often fail due to children's fear and panic, thus a proper sedation procedure that serves to reduce pain and fear is vital for the success of therapeutic procedures in such cases [6, 16].

The objective of this study was to compare the effectiveness of intravenous Ketamine and Dexmedetomidine for children's sedation in ED, and it was well shown that both were quite effective sedation in children. Singh *et al*., [17] concluded that sedation by injection of 8 mg ketamine and 5 mg dexmedetomidine at the same time, was significantly faster. This was in line with our finding that dexmedetomidine sedated children faster than Ketamine alone (sedation time 10 minutes after prescription of the drug was 15 and 10 in Ketamine and Dexmedetomidine groups, respectively), which goes with the findings of this paper. Tammam *et al*., [8] also demonstrated that satisfactory sedation was achieved in a shorter time in the ketamine-dexmedetomidine group in comparison with the dexmedetomidine group, and there was no significant difference between the combined ketamine-dexmedetomidine group and ketamine group. Sedation time was significantly shorter in the combined group as compared to the Ketamine group, which was the same as our findings. Mason *et al*., [18] conducted a study to compare oral midazolam alone or combined with Ketamine as a prodrug before children's surgery. They showed that 7% of their member experienced the loss of blood pressure and transient bradycardia after injection of dexmedetomidine. This adverse event was auto-treated without any medical intervention and was not related to any cardiac issue in the studied children. The present study also had no evidence of side effects from ketamine or dexmedetomidine injections.

Table 3. Patient's vital signs before, during, and after the procedure

Groups	Variables	Times, median (Q1-Q3)[b]					*p* value[a]
		Before Injection	10 minutes after injection	After sedation (Before suturing)	After suturing	After complete orientation	
Ketamine	O2-Saturation%	98 (96-98)	98 (95-98)	98 (95-98)	95 (95-98)	95 (95-98)	0.039
	RR[c] (per minutes)	18 (18-20)	18 (17-19)	18 (17-18)	17 (16-18)	17 (16-18)	0.001
	SBP[c] (mmhg)	97.5 (90-105)	97.5 (90-105)	92.5 (90-100)	92.5 (87-100)	92.5 (90-100)	0.01
	PR[d] (per minutes)	109 (102-115)	105 (100-110)	100 (95-105)	100 (95-105)	95 (92-100)	0.001
Dexmedetomidine	O2-Saturation%	98 (96-98)	95 (95-98)	95 (95-98)	95 (95-98)	96 (95-98)	0.025
	RR[c] (per minutes)	17 (16-18)	17 (16-18)	16 (16-17)	16 (16-17)	16 (16-17)	0.001
	SBP[c] (mmhg)	100 (98-110)	100 (97-107)	100 (92-105)	100 (95-105)	97 (95-105)	0.001
	PR[d] (per minutes)	100 (99-107)	98 (95-102)	96 (95-100)	95 (91-98)	92 (90-95)	0.001

[a] Friedman's test; [b]Q1: 25th Quantile, Q3: 75th Quantile; [c]SBP: Systolic blood pressure; [d]PR: Pulse rate; [e]RR: Respiratory rate. The numbers represent mean calculated by Mann-whitney test.

Sajedi *et al*., [19] showed quicker and more effective sedation by the combination of midazolam in a small dose and ketamine in comparison with the use of midazolam alone, and children behaved much better during venipuncture procedures in the combined group. In addition, the researchers finely demonstrated that children's recovery times in the combined group were shorter than all other groups. The results of this study pointed in the same direction, showing that ketamine and dexmedetomidine had similar effects in sedating children. Although there was significant differences in sedation times during the first 10 minutes up to full recovery, and the results indicated that attending physicians were very satisfied with the sedation process. Follow-up on the members of both groups in terms of vital signs showed no significant difference, and none of the obtained figures fell outside of the normal ranges [7]. Changes in the rest of vital signs were also in line with other studies, requiring no clinical intervention to undo such changes, and this finding demonstrated the small effects of drugs on vital signs, and hence their ignorable side effects.

Generally, the results of this study showed that intravenous ketamine and dexmedetomidine were quite effective in sedating children in ED for either diagnostic or therapeutic procedures. We found that dexmedetomidine could sedate children in shorter times during the first 10 minutes after injection, but eventually Ketamine had a shorter recovery time (from injection to full recovery) in comparison with dexmedetomidine. This study also demonstrated that dexmedetomidine could be used in cases where a shorter sedation time was vital.

Declaration

Ethics approval and consent to participate: The study was carried out with the permission of the Organizational Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.fm.REC.1396.534) and registered as a clinical trial under registration no. IRCT20161226031577N2. Informed consent was obtained from the children's parents or legal guardians before intervention.

Consent for publication: Not applicable.

Conflict of interests: The authors declare that there is no conflict of interest.

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Authors' contributions: Study concept and design by BZK, MF, acquisition of data by MF, ZAS, EVM, analysis and interpretation of data by ZAS, drafting of the manuscript by EVM, HF, critical revision of the manuscript for important intellectual content by all authors.

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