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ORIGINAL ARTICLE

Ketamine, Dexmedetomidine Combination versus Dexmedetomidine in Decreasing Incidence and Severity of Emergence Agitation after Urological Surgeries in Pediatrics under Sevoflurane

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ABSTRACT

Background: Emergence agitation (EA) is a serious complication of recovery from anesthesia. This study aimed to compare the effect of adding ketamine to Dexmedetomidine versus Dexmedetomidine alone in the incidence and severity of EA in pediatric urologic surgeries under sevoflurane anesthesia. **Method:** Prospective Randomized Controlled double blinded clinical study, including a total of 90 pediatric patients of ASA physical status class I and II scheduled for urological surgery were equally divided into 3 groups: Control group (group C) (30 patients) received 10 ml saline; Dexmedetomidine group (group D) (30 patients) received 0.5µg/kg Dexmedetomidine; Ketodex group (group KD) (30 patients) received combination of 0.3µg/kg Dexmedetomidine and 0.15 mg/kg ketamine. Studied drugs were given intravenously 10 minutes before end of anesthesia. **Results:** Dexmedetomidine group and ketodex group had decrease the incidence of emergence agitation it was (23.3%) in dexmedetomidine group and (13.3%) in ketodex group and on other hand (73.3%) in control group and the number of patients requiring midazolam was (16.7%) in dexmedetomidine group and (6.7%) in Ketodex group compared to (60%) in control group. The three groups' respective occurrences of medication side effects were negligible and similar. **Conclusion:** adding ketamine to dexmedetomidine was similar to dexmedetomidine alone in reducing the incidence and severity of emergence agitation in pediatrics urological surgeries under sevoflurane.

Keywords: Ketamine, dexmedetomidine, Postoperative emergence agitation, sevoflurane, urological surgery, pediatrics.

INTRODUCTION

Emergence agitation (EA) in pediatrics is one of most frequent side effects after anesthesia. It occurs in 25- 80 % with a higher prevalence among children aged 2- 6 years of age [1].The risk factors are preschool children, pre-operative anxiety, less soluble volatile anesthetic agents, postoperative pain, abdominal, urological, orthopedic surgeries [2].

For the prophylaxis of EA, combined medication often works better than monotherapy[3].Dexmedetomidine is a potent and highly selective α2 adrenoreceptor agonist, it has described as a sedative, analgesic, sympatholytic without respiratory depression [4].

An antagonist of N-methyl-D-aspartate is ketamine which gained rapid popularity due to its specific properties as protection of upper air way reflexes and potent analgesia[5]. It acts as open channel blocker as it can bind to NMDA receptor preventing ion flow [6].

The aim of this work was to compare the efficacies of IV administration of placebo, Dexmedetomidine, and the combination of Dexmedetomidine and ketamine for reducing the incidence and severity of EA after urological surgery in pediatrics under sevoflurane to determine which has the best outcome and the fewest side effects.

METHODS

This prospective double blinded randomized controlled clinical study was conducted at Zagazig University Hospitals from January 2023 to June 2023 after receiving approval from the local ethics committee (IRB 10453-13-2-2023) and obtained informed consent from parents. The work was done in conformity with the World Medical Association's Code of Ethics (Declaration of Helsinki) for human studies.

As per the research conducted by Abdelhakim et al. [9]. The mean PAED score 30 minutes post-operatively was 3.4 ± 0.9 in the magnesium sulfate group and 3± 1.1 in the ketamine group. Using the Epi Info version 6 tool, the sample size was determined to be 90 pediatric patients at 80% power and 95% Confidence Interval. A total of 95 patients, five patients were excluded as three of them not meeting inclusion criteria, two refused to participate and a computer-generated random table was used to randomly divide them into three equal groups (30 patients in each group) in order to make up for the instances that were dropped. Inclusion criteria were: ASA physical status (PS) classes I and II, aged 3-7 years, both sexes, Body Mass Index (BMI) between 5th to 85th percentile undergoing urological surgeries under sevoflurane with duration of surgery less than 2 hours were enrolled in this study.Patients with history of hypersensitivity to any tested drugs, or with developmental, psychological, or neurological disorders, children with a history of chronic or recent sedative and analgesic drug intake, with cardiac or respiratory diseases and child with sever agitation were excluded from this study.

General anesthesia:After pre-operative evaluation, standard American Society of Anesthesiology (ASA) monitors were connected to the patients: Electrocardiogram (ECG), non- invasive blood pressure (NIBP) and pulse oximetry. Basal hemodynamic and oxygen saturation were recorded.

Sevoflurane mask inhalation was used to produce anesthesia. Once the child was calm, an IV cannula was placed, and injections of 0.01 mg/kg atropine and 1µg/kg fentanyl were administered. Tracheal intubation was made easier with an intravenous infusion of atracurium (0.5 mg/kg).

Anesthesia was maintained with 2-3% sevoflurane in oxygen/air (50%:50%). Ventilation was mechanically controlled throughout surgery adjusted to achieve an end tidal Co2 level about 32-35 mmHg. 10 minutes before end of general anesthesia, all tested drugs were given intra venous. Intravenous treatment of a combination of 0.05 mg/kg neostigmine and 0.01 mg/kg atropine sulphate eliminated the residual effects of atracurium.After extubation, all patients were shifted to post anesthetic care unit (PACU) and monitored for heart rate, blood pressure, SpO2 for first 6 hours postoperatively, paracetamol (10 mg/kg) was given intravenously for analgesia.

The patients were randomly allocated into three groups by computer generated random number table which was sealed in opaque envelope:Control group (Group C) (30 patients): received 10 ml of normal saline as placebo.Dexmedetomidine group (Group D) (30 patients): received 0.5µg/kg of dexmedetomidine diluted to 10 ml with normal saline.Ketodex group (Group KD) (30 patients): received both 0.3 µg/kg dexametomedine plus 0.15mg/kg ketamine diluted to 10 ml with normal saline.

For blindness, one of the authors was responsible for giving the tested drug and other one unaware of the given drug was responsible for data collection. Also, patients were blind to group assignment.

Incidence of preoperative Emergence Agitation (EA): by 5 point scale as child with score ≥ 4 is considered to be agitated (Table 1)[7].

Throughout the 1st 6 hours postoperatively, the following were recorded:

Incidence of post-operative Emergence Agitation (EA): by five points scale as child with score ≥ 4 was considered to be agitated (Table 1)[7].

Severity of Emergence Agitation (EA): is evaluated and recorded every 30 min in the 1st hour and then every hour in the next 5 hours by using Pediatric Anesthesia emergence Delerium scale (PAED scale) as mild if score was ≥ 10, moderate ‹ 16 and sever ≥ 16 (Table 2)[8].There were records of the occurrences of side effect such as bradycardia, tachycardia, hypotension, hypertension, nausea, and vomiting.

Statistical analysis:Verification, input, and analysis of data were done with SPSS version 20. Quantitative values were expressed as mean ± SD, whereas qualitative values were expressed as numbers and percentages. Qualitative values were statistically analyzed using the Chi square test (X2). For the statistical analysis of quantitative values, the Kruskal Wallis test or ANOVA were employed. P-values less than 0.05 and less than 0.001 indicate significant and very significant differences, respectively.

RESULTS

A total of 95 patients were scheduled for urological surgeries under sevoflurane anesthesia. Five patients were excluded as three of them not meeting inclusion criteria, two refused to participate (Fig. 1).

All the 90 patients in the three groups were comparable regarding age, sex, BMI, ASA and duration of surgery (Tab 3).Statistically, there was no significant difference in fivepoint agitation scale between studied groups pre-operative. However, it was highly significant in group C compared to group D and group KD (p=0.0001) post- operative. The incidence of agitation was statistically significant in group C compared to group D and group KD (p=0.0001) with no statistical difference between group D and group KD

(Tab 4).

The severity of emergence agitation by PAED scale was statistically significant higher in group C compared to group D and group KD in 30 min, 1,2 and 3hours post-operative (P=0.0001) with no statistical difference between group D and group KD Otherwise, there was no statistically significant difference between the three studied groups at 4, 5, 6 hours postoperative p>0.05 (Tab.5).

The number of patients (%) in groups D and KD who required midazolam as a rescue medication for EA within the first 24 hours after surgery was statistically significantly lower than that of group C (p1=0.003, p2=0.0001), respectively. It was similar in group D to that in group KD (p3=0.14) (Tab.6)

The three groups' respective incidences of the various related side effects were negligible as bradycardia, tachycardia, hypotension and vomiting and statistically similar (Fig.2)(Tab.7).

Table (1): Fivepoints agitation scale [7]

SCORE	Behavior
1	Sleepy
2	Awake and calm
3	Irritable and crying
4	Inconsolable crying
5	Sever restlessness

Table (2): Pediatric anesthesia emergence delirium scale (PAED) [8]

Behavior	Not at all	Just a little	Quite a bit	Very much	Extremely
Make eye contact with caregiver	4	3	2	1	0
Actions are purposeful	4	3	2	1	0
Aware of surrounding	4	3	2	1	0
Restless	0	1	2	3	4
Inconsolable	0	1	2	3	4

Table(3): Demographic data and duration of surgery in studied groups:

Variable	Group C n=30	Group D n=30	Group KD n=30	f	p
Age (year) Mean ±SD range	4.07±1.17 3-6	4.9±1.47 3-7	4.5±1.38 3-7	4.08	0.091
Sex Male female	18(60%) 12(40%)	21(70%) 9(30%)	24(80%) 6(20%)	2.86	0.240
BMI (kg/m²) Mean ±SD range	16.69±1.22 14.87-19.32	16.02±1.73 13.98-19.32	16.18±1.82 13.87-19.30	1.420	0.247
ASA	1 (100.0)	1 (100.0)	1 (100.0)	-	-
Duration of operation(min) Mean ±SD Range	67.7±7.63 57-85	71.93±11.37 56-90	72.9±11.91 57-90	2.089	0.13

P1=Group C vs Group D, P2=Group C vs Group KD, P3= Group D vs Group KD.
Data were expressed as range and Mean ±SD. [SD=standard deviation]or number and percentage.fanova test. p≥0.05 was considered no significant. p<0.05 was considered significant. BMI: body mass indexBMI: Body mass index.ASA: American Society of Anesthesiologist

Table (4): Pre and post-operative five point scale for of agitation in studied groups:

Five point scale	Pre-operative				Post-operative			
	Group C n=30	Group D n=30	Group KD n=30	P	Group C n=30	Group D n=30	Group KD n=30	P
1	3(10%)	5(16.7%)	5(16.7%)		0	3(10%)	5(16.7%)	
2	22(73.3%)	21(70%)	23(76.7%)	1.97 c 0.74	6(20%)	11(36.7%)	13(43.3%)	0.0001
3	5(16.7%)	4(13.3%)	2(6.7%)		2(6.7%)	9(30%)	8(26.7%)	
4	0	0	0		14(46.7%)	7(23.3%)	4(13.3%)	
5	0	0	0		8(26.6%)	0	0	
Incidence of agitation post-operative					22(73.3%)	7(23.3%)	4(13.3%)	*P1=0.0001 *P2=0.0001 P3=0.32

P1=Group C vs Group D, P2=Group C vs Group KD, P3= Group D vs Group KD.

Table (5):Pediatric Anesthesia Emergence Delirium (PAED) scale in studied group:

PAED Scale	Group C n=30	Group D n=30	Group KD n=30	F	p
PAED 30 min Mean ±SD range	12.03±1.9 10-17	8.57 ±0.82 7-10	8.13 ±0.78 6-9	84.1	*P1= 0.0001 *P2= 0.0001 P3=0 .19
PAED 1hr Mean ±SD range	13.13±1.72 10-17	10.83±2 6-17	10.33±1.81 5-16	19.64	*P1=0 .0001 *P2 =0.0001 P3= 0.29
PAED 2hr Mean ±SD range	10.57±2.08 7-16	6.9±0.78 6-9	6.0±0.49 5-7	103.5	*P1= 0.0001 *P2=0 .0001 P3=0 .09
PAED 3 hr Mean ±SD range	7.2±1.6 6-12	6.5 ±0.78 5-8	5.8±0.66 5-7	13.23	*P1= 0.009 *P2=0 .0001 P3=0 .08
PAED 4 hr Mean ±SD range	6.2±1.5 4-10	6±0.98 4-8	5.5±1.04 4-7	2.93	0.058
PAED 5 hr Mean ±SD range	5.2±1.23 3-8	4.9±1.01 3-7	4.5±1.00 3-6	2.88	0.061
PAED 6 hr Mean ±SD range	4.1±1.09 2-6	3.9±0.96 2-5	3.5±1.01 2-5	2.68	0.074

P1=Group C vs Group D, P2=Group C vs Group KD, P3= Group D vs Group KD.

Table (6): Midazolam requirement in studied groups

Midazolam requirement in mg	Group C n.30	Group D n.30	Group KD	$\chi 2$	p
	N(%)	N(%)	N(%)		
Needed Not needed	18 (60%) 12(40%)	5(16.7%) 25(83.3%)	2(6.7%) 28(93.3%)	22.7	*P1=0 .003 *P2=0 .0001 P3=0 .14
Midazolam dose(mg) Mean ±SD	1.5±0.5	1±0	1±0	KW 8.3	*P1=0.008 *P2=0.008 P3= 1

P1=Group C vs Group D, P2=Group C vs Group KD, P3= Group D vs Group KD.

Table (7): Complications in studied groups

complication	Group C n=30	Group D n=30	Group KD n=30	P
	N(%)	N(%)	N(%)	
Bradycardia	0.0	4(13.3%)	2(6.7%)	0.612
Tachycardia	2(6.7%)	0.0	0.0	0.49
Hypotension	0.0	3(10.0%)	1(3.3%)	0.671
Vomiting	1(3.3%)	0.0	0.0	0.99

DISCUSSION

Multiple drugs were studied to reduce EA, among these drugs dexmedetomidine which provides better sedation and analgesia with no respiratory depression[10]. Also, ketamine is NAMD receptor antagonist which has amnestic, analgesic, and hypnotic effects [11].

In this study we found that dexmedetomidine alone is similar to ketodex as regarding incidence and severity of emergence agitation and needed of rescue medication with less adverse effect in pediatric patient undergo urological surgeries under sevoflurane anesthesia.

In this study there was no statistically significant difference between groups regarding age, sex, BMI, ASA, classification, duration of surgery and recovery time.

Also, in this study regarding the incidence of preoperative agitation by use of five point scale, there was no statistically significant difference between dexmedetomidine group, ketodex group and control group. But regarding incidence of postoperative agitation by use of five points scale, There was statistically significant differences between the groups as it was higher in control group followed by dexmedetomidine group then ketodex group and no statistically significant differences between dexmedetomidine group and ketodex group. That was in agreement with Azizkhani et al[12] who compared The effects of dexmedetomidine and propofol in reducing recovery agitation in pediatric patients following ketamine procedural sedation in the emergency department and found a statistically significant difference in the incidence of agitation between the groups, with the incidence of agitation being lower in the ketodex group than in the ketofol group and the ketamine group.

Also, Isik et al[13]reported that dexmedetomidine reduces emergence agitation in pediatric patients who have undergone sevoflurane anesthesia. The incidence of emergence agitation differed statistically substantially across the groups, with the dexmedetomidine group experiencing less of it than the control group.Beside,Guler et al[14] examined after juvenile adenotonsillectomy, a single-dose dexmedetomidine decreases agitation and facilitates a smooth extubation compare to placebo group. An intravenous bolus of 0.5µg/kg dexmedetomidine administered five minutes before to the completion of surgery was reported to lower the incidence of postoperative emerging agitation.

In this study the severity of EA by using this analysis of the pediatric anesthesia emergence delirium scale (PAED) revealed a statistically

significant difference between the control group (C) and dexmedetomidine groups (D) and between control and ketodex (KD) groups in severity of EA at 30min, 1 hour, 2 hour and 3 hour post operative with no statistically significant difference between (D) and (KD) groups. Otherwise, there was no statistically significant difference between the three studied groups at 4, 5and 6 hours postoperative.

It was agreement with Hadi et al[15] who found that the PAED scale score at 1 hour postoperative was significantly lower in the ketodex in comparison to the control. Also Abdelzaam&Mahdy [16] found that postoperative, at 10 minutes, 20 minand 30 min PAED scale was lower in ketamine group and dexmedetomidine group than control group.

Chen et al[17] found that the peak PAED scale scores for emergence agitation was statistically significant lower in the dexmedetomidine and ketamine groups than in the control group which was in a line with our results.

In our study regarding the midazolam requirements, we found that there was statistically significant higher midazolam needed in control group compared to dexmedetomidine group and ketodex group. It was agreement with Azizkhani et al[12] who found that ketodex decreased midazolam needed.

In this study as regard complication there was no significant differences between groups regard the occurrence of bradycardia, tachycardia, hypotension and vomiting. Which in agreement with the study of Hadi et al[15] who reported that the administration of ketodex did not cause any adverse effects, including bleeding, postoperative respiratory depression, bradycardia, laryngospasm, bronchospasm, vomitingor hypotension.

Kim et al[18] found that the ketodex group presented a lower complication rate than the midazolam group including oxygen desaturation and hypotension. But is contrast with Azizkhani et al[12] who Found that the transient hypotension occurred with ketodex group, may be due to intra venous dexmedetomidine with dose 0.7µg/kg and ketamine with dose 1mg/kg which was approximately doubled the dose used in our study.

The limitations of the present study:The second 24 hours following surgery were not used to assess the effects of the medications under study. The participants in this study were restricted to pediatric patients (ages 3-7 years) receiving urological procedures who were in ASA physical status class I or II. For each substance under test, just one dosage is assessed.

CONCLUSION

Dexmedetomidine (0.5µg/kg) alone is similar to ketodex (ketamine 0.15mg/kg-dexmedetomidine 0.3µg/kg) in reducing the incidence and severity of EA with minimally associated side effects.

Recommendation Performing further studies with large number of patients on different type of surgeries in multi-center to confirm our finding. Encouraging the anesthesiologist to use dexmedetomidine (0.5µg/kg) alone is recommended for prevention of EA in urological surgeries.

Declaration of interest

The authors report no conflicts of interest. The authors along are responsible for the content and writing of the paper.

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