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ORIGINAL ARTICLE

Dexmedetomidine–ketamine and midazolam–ketamine combinations for sedation in pediatric patients undergoing extracorporeal shock wave lithotripsy: a randomized prospective study

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Abstract
Purpose Extracorporeal shock wave lithotripsy (ESWL) requires sedation in pediatric patients. Dexmedetomidine is a relatively new agent used for sedation. The aim of this randomized prospective study was to compare the effects of dexmedetomidine–ketamine and midazolam–ketamine combinations on the recovery time, hemodynamic and respiratory variables, and side effects in pediatric patients undergoing ESWL.
Methods Fifty pediatric patients aged between 2 and 15 years who were scheduled for elective ESWL were randomized into two groups. In Group D we applied dexmedetomidine at1 μg/kg, given over 10 min, and a bolus of 1 mg/kg ketamine for sedation. In Group M we applied midazolam at a 0.05 mg/kg bolus dose 10 min before the procedure and a 1 mg/kg bolus of ketamine. We measured and monitored the hemodynamic variables, oxygen saturation, and recovery time, and we also monitored the side effects.
Results Four patients in group D refused to complete the study; 21 patients in group D and 25 patients in group M completed the study. We found the recovery time [eye-opening time (9.3 ± 4.5 vs. 16.2 ± 6.5 min; $p < 0.001$), verbal response time (12.8 ± 4.9 vs. 19.2 ± 7.2 min; $p < 0.001$), and the cooperation time (17.1 ± 5.0 vs. 23.3 ± 7.7 min; $p < 0.001$)] to be shorter in the dexmedetomidine group. Also, the heart rate values were lower in the dexmedetomidine group at the 20th minute of the procedure (99.1 ± 19.0 vs. 118.7 ± 7.3 beats/min; $p = 0.016$).
Conclusion In this study we found the recovery time to be shorter, with hemodynamic stability, in the dexmedetomidine group, compared with the midazolam group. So we can conclude that dexmedetomidine may be a good and safe alternative agent for sedation, with a shorter recovery period than midazolam, in the pediatric population.

Keywords Dexmedetomidine · Sedation · ESWL · Pediatrics

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Introduction

Extracorporeal shock wave lithotripsy (ESWL) is used for the treatment of urinary tract stones [1]. Nowadays more than 80% of urinary tract stones are managed by this method. It can be used safely in pediatric patients also [2, 3]. It is a noninvasive technique, but the shock waves cause transient deep sharp pain and visceral discomfort. So analgesia and sedation is usually required during the procedure. Several anesthetic agents and modalities have been used for this purpose [4, 5]. The anesthetic agent should be hemodynamically safe and provide adequate analgesia, sedation, and immobility level. Most of the anesthetics or analgesics/sedatives used cause adverse effects during the ESWL procedure. They may cause prolonged sedation, hemodynamic instability, and prolonged hospital stay.

Ketamine is one of the most commonly used agents for sedation in ESWL. It can be used alone or in combination to achieve ideal sedation. Combining it with other agents may result in deep enough sedation and a reduction in adverse effects [6]. Midazolam has both sedative and anxiolytic effects and it is used for sedation in invasive and

noninvasive procedures. It also improves compliance in the induction of anesthesia. Midazolam is safely used in outpatient pediatric groups for effective sedation and reduced anxiety. It has a minimal effect on recovery time [7]. Both midazolam and ketamine have been used for sedation in pediatric patients for different procedures. Jobeir et al. [8] used ketamine and/or midazolam in pediatric patients for sedation during cardiac catheterization. They found that the combination in small doses was safe in children.

Dexmedetomidine, a relatively new agent, is a highly selective alpha-2 receptor agonist and it has both sedative and analgesic effects [9, 10]. Administering dexmedetomidine intraoperatively reduces anesthetic requirement, shortens the postoperative recovery period, and blunts the sympathetic response due to surgical stimulation [11]. Because of these effects, dexmedetomidine may be a suitable agent for conscious sedation for ESWL, which is a mildly painful procedure. There are not many studies of dexmedetomidine use in the pediatric population [12, 13]. The aim of this study was to compare the effects of a dexmedetomidine–ketamine combination and a midazolam–ketamine combination on hemodynamics; analgesic, sedative, and respiratory effects; and the recovery period in pediatric patients undergoing ESWL. The primary outcome measure of this study was the recovery period parameters (eye-opening time, verbal response time, cooperation time, and achievement of an Aldrete score of 8). The secondary outcome measure was the analgesic/sedative effect of the dexmedetomidine–ketamine combination compared with that of the midazolam–ketamine combination. We hypothesized that dexmedetomidine would provide a shorter recovery period than midazolam.

Patients, materials, and methods

This randomized, prospective study was done after University ethics committee (Gaziantep University, Gaziantep, Turkey) approval was given. We obtained assent from the children and written informed consent from all parents. Fifty pediatric patients aged between 2 and 15 years, who were scheduled for elective ESWL, were enrolled in the study. All patients had American Society of Anesthesiologists (ASA) I or II physical status. Exclusion criteria were current respiratory or psychiatric disorder, allergy to any medications used in the study, second- or third-degree heart block, or chronic use of an alpha-2 agonist. All patients were scheduled for ESWL electively. All had a single renal stone and no pain. None of the patients had a history of previous ESWL. On their arrival at the ESWL unit an IV catheter was placed and all patients were monitored with ECG, noninvasive blood pressure, oxygen saturation (SpO_2), and respiratory rate. An infusion of NaCl solution (0.9%) was started at the rate of 100 ml/kg/day in all patients. The basal values for heart rate (HR), mean arterial blood pressure (MAP), respiratory rate (RR), and SpO_2 were recorded (BSM 2301K; Nihon Kohden, Tokyo, Japan) just before the administration of the study drug. The values were recorded at baseline, after sedation, and every 5 min thereafter. The patients were randomized into two groups by a closed envelope method. Four patients in the dexmedetomidine group refused to complete the study, so they were excluded. In Group D ($n = 21$) dexmedetomidine and ketamine were used for sedation. The patients received 1 μg/kg of dexmedetomidine given over 10 min and a 1 mg/kg bolus of ketamine for sedation. In Group M ($n = 25$) patients received midazolam at a 0.05 mg/kg bolus dose 10 min before the procedure and a 1 mg/kg bolus of ketamine. After the initial drugs were administered, one of the authors (S.K.) left the patients, and they were followed up by two other anesthetists (A.M. and R.G.) who were blind to the drug regimen. The patients were followed and evaluated by using the Ramsay sedation score (RSS) [14]. An RSS of 4 is accepted as an adequate sedation level. Additional ketamine at a dose of 1 mg/kg was used as needed (patient movement or crying) in both groups. When we achieved an RSS of 4 the ESWL procedure was started. All patients breathed fresh room air. When oxygen desaturation ($SpO_2 < 92\%$) occurred oxygen was supplemented at 4 l/min via a nasal canula and continued until the ESWL was completed. The sedation score (RSS) and the hemodynamic (MAP, HR) and respiratory (RR, SpO_2) variables were recorded every 5 min during the ESWL procedure by another anesthetist (F.Y.). After the termination of ESWL, the recovery time and the awakening were evaluated with the Aldrete score by another anesthetist (E.K.), who did not take part in the operating room care. The main outcome measurement was the recovery parameters (eye-opening time, verbal response time, cooperation time, and time interval between the end of the procedure and the achievement of an Aldrete score of 8) [15]. Adverse effects such as bradycardia (above 20% decrease compared with baseline), hypotension (MAP <50 mmHg), desaturation ($SpO_2 < 92\%$), and nausea/vomiting were also recorded during the procedure. Atropine 0.01 mg/kg IV for bradycardia, 0.9% NaCl infusion at 1–3 ml/kg/h for hypotension (stopped when a MAP value of 50 mmHg occurred), and nasal oxygen supply for desaturation were the treatments applied. As management of the adverse effects of upper airway obstruction (noted by both SpO_2 and observation) jaw thrust and the application of an airway was planned, and for hypersalivation, suction was planned.

The software program SPSS 13.0 for Windows (SPSS, Chicago, IL, USA) was used for statistical analysis. In our preliminary study, after interim analysis, we found a

shorter recovery period with dexmedetomidine (according to the cooperation time, which was 28.9 ± 5.8 min for midazolam and 12.7 ± 2.3 min for dexmedetomidine). Using these data, a power analysis was done to calculate sample size and it was found that 14 patients were needed for each group to achieve results with a power of 90% (for $\alpha = 0.05$). We planned the study with 25 patients in each group. The statistical analysis of differences between two groups was done with unpaired Student's *t* test. Categorical data were analyzed by using Fisher's exact test or the χ^2 test. Repeated measure of analysis of variance was used for serial data. Data are presented as means ± standard deviation. A *p* value of <0.05 was considered as statistically significant.

Results

Fifty patients were enrolled in the study. There were 21 patients in Group D (age 9 ± 3.9 years, 13 male) and 25 patients in Group M (age 7.2 ± 4.2 years, 11 male). Four patients in the dexmedetomidine group refused to complete the study and they were excluded from the analysis. The demographic parameters and ASA physical status of the patients in the two groups were similar. There was no statistically significant difference between the groups in preoperatively measured hemodynamic and respiratory variables. Also, the parameters of ESWL such as voltage (15.5 ± 1.2 in group M vs. 15.4 ± 1.3 kV in group D), total operation time (17.0 ± 6.4 min in group M vs. 16.1 ± 3.5 min in group D), and stone localization were similar in the two groups. The demographic and operational variables are shown in Table 1. When the groups were compared according to recovery time with the Aldrete score, there was no statistically significant difference between the groups. The times to reach an Aldrete recovery score of 8 were similar (17.4 ± 6.5 min in group M vs. 16.7 ± 6.3 min in group D; $p > 0.05$). But eye-opening, verbal response, and cooperation times were significantly shorter in the dexmedetomidine group (Table 2). Both drug regimens showed similar efficacy in analgesia/sedation. None of the patients in the dexmedetomidine group and three in the midazolam group (12%) required additional ketamine, but this difference was not statistically significant ($p = 0.101$). Both groups had similar average RSS values during the ESWL procedure. Respiratory rates (RR) at baseline, and peri- and postprocedurally were similar in both groups. Baseline HR, MAP, SpO_2, and RR were not significantly different between the groups. But in the dexmedetomidine group the HR was significantly lower than that in the midazolam group at the 20th minute of the procedure (99.1 ± 19.0 vs. 118.7 ± 7.3 beats/min; $p = 0.016$) (Fig. 1). In the midazolam group the HR and MAP values were similar during the procedure compared with the baseline values. In the dexmedetomidine group the MAP values during the procedure were also similar compared with the baseline. But the HR was significantly lower after the premedication (106.6 ± 22.9 beats/min) and at the 20th minute of the procedure (99.1 ± 19.0 beats/min) compared with the baseline (111.9 ± 23.8 beats/min; $p = 0.009$ and $p = 0.007$, respectively). The HR at the 20th minute of the procedure was also lower than the after-premedication values in Group D ($p = 0.014$). Mean oxygen saturation rates were similar in the two groups at all

Table 1 Demographic variables in the groups

	Group D ($n = 21$)	Group M ($n = 25$)	*p* value
Age (years)	9.0 ± 3.9	7.2 ± 4.2	>0.05
Sex (M:F)	13:8	11:14	>0.05
ASA physical status I	1 (4.7%)	2 (4%)	>0.05
ASA physical status II	20 (95.3%)	23 (96%)	>0.05
Maximum voltage (kV)	15.4 ± 1.3	15.5 ± 1.2	0.271
Stone localization (renal:ureter)	16:5	18:7	0.747
Operation time (min)	16.1 ± 3.5	17.0 ± 6.4	>0.05

ASA American Society of Anesthesiologists

Table 2 Recovery time variables in the groups

	Group D ($n = 21$)	Group M ($n = 25$)	*p* value
Time to reach Aldrete score of 8 (min)	16.7 ± 6.3	17.4 ± 6.5	>0.05
Eye-opening time (min)	9.3 ± 4.5	16.2 ± 6.5	<0.001
Verbal response (min)	12.8 ± 4.9	19.2 ± 7.2	<0.001
Cooperation time (min)	17.1 ± 5.0	23.3 ± 7.7	<0.001

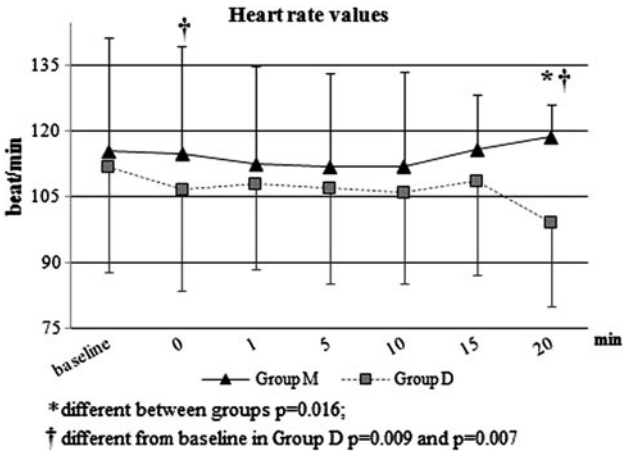

Fig. 1 Changes in heart rate values in the two groups

Table 3 Side effects recorded in patients

	Group D ($n = 21$)	Group M ($n = 25$)	p value
Nausea/vomiting	1 (4.7%)	8 (32%)	0.020
Hypotension	1 (4.7%)	0 (0%)	0.270
Hypertension	2 (9.5%)	2 (4%)	0.855
Bradycardia	0 (0%)	0 (0%)	>0.05
Tachyarrhythmia	1 (4.7%)	1 (4%)	0.900
Shivering	0 (0%)	4 (8%)	0.055
Additional ketamine need	0 (0%)	2 (12%)	0.101

times ($p > 0.05$). The side effects were evaluated and the incidence of nausea/vomiting was higher in Group M (32 vs. 4.7%; $p = 0.02$). The incidences of other side effects were similar in Groups D and M, respectively; hypotension (4.7 vs. 0% $p = 0.270$), hypertension (9.5 vs. 4%; $p = 0.855$), and shivering (0 vs. 8%; $p = 0.055$). No episode of bradycardia was detected in either of groups. Tachyarrhythmia was seen in one patient in each groups. The side effects recorded in the two groups are listed in Table 3.

Discussion

The aim of this study was to compare the effects of a dexmedetomidine–ketamine combination and a midazolam–ketamine combination on hemodynamics; analgesic, sedative, and respiratory effects; and the recovery period in pediatric patients undergoing ESWL.

Extracorporeal shock wave lithotripsy (ESWL) is an effective and safe method for the treatment of upper urinary tract stones, but it can cause pain and discomfort in many patients. This treatment is also used safely in pediatric patients, but sufficient sedation is necessary [4].

Ketamine is a sedative analgesic agent that does not induce clinically important respiratory depression or hemodynamic instability. It also induces better sedation/analgesia and maintenance of airway reflexes than other commonly used agents [16, 17]. Monk et al. [17] compared midazolam–alfentanil and midazolam–ketamine combinations in lithotripsy and reported that ketamine infusion provided better hemodynamic and respiratory stability intraoperatively but it was associated with more disruptive movements. Despite these benefits, its use in children is associated with prolonged recovery time and emergence delirium [18]. Ketamine was used for sedation in adult ESWL patients [4]. It is also frequently used in pediatric patients undergoing cardiac catheterization [19, 20]. In a randomized prospective study done with pediatric ESWL patients [4], the patients were divided into two groups, who received ketamine 2 mg/kg in one group and propofol 3 mg/kg and fentanyl 1 μg/kg in the other. The authors of that study found the procedure and discharge times to be similar in the two groups. The recovery time was longer in the ketamine group (38.9 ± 19.1 vs. 19.2 ± 11.3 min; $p < 0.05$). This may have been due to the ketamine dose used (2 mg/kg). In our study we used ketamine at a lower dose (1 mg/kg) because of the combination.

Dexmedetomidine is a selective alpha-2 adrenoreceptor agonist which has a rapid onset and relatively short elimination half-life. It has a lower risk of respiratory depression. It may cause hypotension, bradycardia, and transient hypertension with a loading dose [21]. The analgesic effect of dexmedetomidine has been shown in different studies [22, 23]. Midazolam and dexmedetomidine caused a mild decrease in MAP which did not require any medication. The combination of dexmedetomidine with other anesthetic agents can be useful for sedation and can be an alternative to the frequently used midazolam or propofol [5, 24]. Dexmedetomidine is frequently used at a 1 μg/kg dose given over 10 min as the initial dose, as we did in our study. In the study of Alhashemi and Kaki [24] they found that dexmedetomidine was a safe and effective drug for sedation during ESWL. They also demonstrated that dexmedetomidine and propofol sedations were comparable. They found higher SpO_2 values, slower respiratory rate (RR), and lower visual analogue scale (VAS) pain scores in their dexmedetomidine group. In our study we observed similar SpO_2 levels and no desaturation in the two groups. These findings suggest that dexmedetomidine, as a sedative drug, may provide advantages over propofol during ESWL.

Dexmedetomidine affects sympathetic ganglia and produces sympatholytic results. So it produces dose-dependent decreases in blood pressure [25, 26]. In a study, dexmedetomidine was used for sedation in an outpatient pediatric population and produced unpredictable effects on blood pressure, HR, and electrocardiogram [27]. The hemodynamic effects of dexmedetomidine in healthy populations are also well described. There is a biphasic response to this drug. First an initial increase in blood pressure and a reflex decrease in HR occurs. After stabilization, the HR and blood pressure return to baseline values (not more than 20% compared with baseline; 94.7 ± 6 vs. 100 ± 7 mmHg for blood pressure and 57 + 1 vs. 62 ± 9 beats/min for HR, respectively) [28]. Despite the deep sedation, it does not cause severe concomitant respiratory effects because of its alpha-2 adrenergic agonism. In another study, the authors compared dexmedetomidine and propofol and found that dexmedetomidine produced minimal cardiovascular and respiratory side effects [29]. In our study no episodes of bradycardia, hypotension, or oxygen desaturation were noted in any of the patients who received dexmedetomidine.

Dexmedetomidine is superior to standard barbiturates and hypnotics because of its short half-life of about 1.5–3 h after intravenous injection [30]. This short half-life makes it easier to titrate and faster to recover. Because of its short half-life and lack of respiratory side effects it is used safely in pediatric patients for sedation. In our study we found eye-opening, verbal response, and cooperation times to be shorter in the dexmedetomidine group. This is comparable with results in the literature [31–33].

In our study, the only side effect that was more frequent in the midazolam group was nausea/vomiting (32 vs. 4.7%; $p = 0.02$). Other side effects such as hypotension, hypertension, bradycardia, tachycardia, shivering, and additional ketamine need were similar in the two groups. These findings were similar to those in the literature.

In conclusion, we found that both dexmedetomidine and midazolam drugs had satisfactory sedative and analgesic effects and were well tolerated. In the dexmedetomidine group the recovery times were shorter and the HR values were lower than those in the midazolam–ketamine group. So we can conclude that dexmedetomidine may be a good and safe alternative agent for sedation, with a shorter recovery period than midazolam, in the pediatric population.

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