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ORIGINAL ARTICLE

IV paracetamol effect on propofol–ketamine consumption in paediatric patients undergoing ESWL

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Abstract
Purpose Electroshock wave lithotripsy (ESWL) is a painful procedure performed with sedoanalgesia in paediatric patients. The propofol–ketamine combination may be the preferable anaesthesia for this procedure, and propofol–ketamine consumption may be decreased with the administration of intravenous (IV) paracetamol. In this study we investigated the effect of IV paracetamol administration on propofol–ketamine consumption, recovery time and frequency of adverse events in paediatric patients undergoing ESWL.
Methods Sixty children, ranging in age from 1 to 10 years and with American Society of Anesthesiologists Physical Status 1–2, were included in this prospective, randomized, double-blinded study. Thirty minutes prior to the procedure children randomly assigned to Group I received IV 15 mg/kg paracetamol, and those randomly assigned to Group II received 1.5 mL/kg IV saline infusion 30 min. The propofol–ketamine combination was prepared by mixing 25 mg propofol and 25 mg ketamine in a total 10 mL solution in the same syringe. After the administration of 0.1 mg/kg midazolam and 10 μg/kg atropine to both groups and during the procedure, the propofol–ketamine combination was administered at 0.5 mg/kg doses to achieve a Wisconsin sedation score of 1 or 2. Oxygen saturation and heart rate were recorded at 5-min intervals. Propofol–ketamine consumption, recovery times and adverse events were also recorded.
Results Demographic data were similar between groups. Propofol–ketamine consumption (Group I, 25.2 ± 17.7 mg; Group II, 35.4 ± 20.1 mg; $p = 0.04$) and recovery times (Group I, 19.4 ± 7.9 min; Group II, 29.6 ± 11.4 min; $p < 0.0001$) were significantly different between groups. Saturation, heart rate and adverse events were similar in both groups.
Conclusion Our data suggest that the administration of IV paracetamol decreases propofol–ketamine consumption for adequate sedation during ESWL procedures in paediatric patients and shortens recovery time.

Keywords ESWL · Propofol · Ketamine · Paracetamol

Introduction

Electroshock wave lithotripsy (ESWL) is the management of choice for the treatment of urinary tract stones. It is a safe and non-invasive technique but causes transient, deep and sharp pain with visceral discomfort [1]. The goal of anaesthetic management during ESWL is to provide adequate analgesia in addition to safe sedation modalities, immobility and cardiovascular stability. For this purpose, opioids, benzodiazepines, barbiturates, ketamine, propofol, acetaminophen, and local and topical anaesthetics are commonly used drugs during ESWL. In addition to thoroughgoing analgesia, the level of sedation in children should be notably deeper than that in adult patients in order to prevent any psychological trauma to the child. However, the wide variability in dose response to sedatives by children may increase the frequency of respiratory and cardiovascular complications in this patient population [2, 3].

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The characteristics of an ideal medication and the proper technique for moderate sedation during ESWL should include a rapid onset of action and a duration of action sufficient for the procedure, as well as allowing a rapid recovery with minimal adverse effects [4, 5]. Combination regimens have been shown to be superior to single agents, providing different degrees of patient comfort and procedural success during sedation procedures depending on the specific combination. Within this framework, propofol–ketamine combinations in particular have gained popularity for this purpose.

Propofol has been increasingly used outside of operating room settings due to its rapid onset, short duration of action and association with a smooth recovery of the patient; when titrated properly, it can be successful in establishing conditions that allow short-lived procedures to be completed without difficulty. The combination of ketamine at subanaesthetic doses with propofol for procedural sedation and analgesia at lower doses of each agent may result in a reduction of undesirable adverse effects of both agents while maintaining optimal conditions for performing the procedure.

Opioids, however, especially when used in combination with sedative–hypnotics, may produce clinically significant respiratory depression and increase the incidence of nausea and vomiting. For this reason, opioids are generally avoided during ESWL. Thus, intravenous (IV) paracetamol with a high tolerability profile may be used as the analgesic component of an alternative combination strategy during a painful procedure, such as ESWL [6, 7]. Paracetamol has a centrally acting analgesic mechanism and generally preferred for the treatment of in mild to moderate pain. The addition of paracetamol to combination regimens would be advantageous as it would reduce sedative agent consumption during painful procedures and contribute to a desirable and safe anaesthesia target profile. The aim of this study was to investigate the effect of the administration of IV paracetamol on propofol–ketamine consumption, recovery period and adverse effect profile during ESWL.

Materials and methods

This study was approved by Baskent University Institutional Review Board and Ethics Committee (Project no: KA09/240) and supported by Baskent University Research Fund. Informed consent for sedation and ESWL was obtained from the patients' parents. Sixty children diagnosed with urinary tract stones, with American Society of Anesthesiologists (ASA) Physical Status 1–2 and ranging in age from 1 to 10 years, scheduled to undergo ESWL with sedation were recruited in this randomized, double-blind, prospective clinical study. All of the patients were admitted to hospital on the day before the procedure. Prior to sedation, a brief physical examination, history of present illness and past medical history and review of systems were conducted.

All patients had only one renal stone without pain, and none of them had undergone a previous ESWL procedure. Exclusion criteria for the study included severe asthma, upper airway infection, chronic pulmonary disease, cardiovascular and renal disease, muscular and metabolic disease, neurodegenerative disease and craniofacial malformations. Prior to the study, sealed envelopes from a computer-generated table were prepared by a nurse who was not associated with the study, and the envelopes were opened by the investigators just before the infusion.

Patients were randomly divided into two groups , with Group I ($n = 30$) patients receiving 15 mg/kg IV paracetamol and Group II ($n = 30$) patients receiving an IV infusion of NaCl solution at a rate of 1.5 mL/kg 30 min before the initiation of ESWL. The patient characteristics, including age, sex, weight and ASA physical status, were recorded prior to sedation by an anaesthesiologist who was blind to the study protocol. After IV catheter placement under EMLA in the non-dominant hand of all patients, the IV paracetamol or saline infusion was started according to the randomization sequence.

The propofol–ketamine combination was prepared by mixing 25 mg of 2% propofol and 25 mg of ketamine in 10 mL of solution in the same syringe (2.5 mg propofol and 2.5 mg ketamine in 1 mL). All patients received 0.1 mg/kg midazolam and 10 μg/kg atropine as premedication before being transferred to the ESWL room. Sedation levels were evaluated by the Children's Hospital of Wisconsin Sedation Scale (CHWSS) (Appendix 1). After the initial sedation with midazolam, propofol–ketamine was administered at 0.5 mg/kg doses as required during the procedure to achieve a Wisconsin sedation score of 1 or 2. The total amount of propofol–ketamine consumption for the whole procedure was recorded in millilitres, then altered to milligrams; per body weight consumption was also calculated for each sedative. The sedation procedure was carried out by an anaesthesiologist blind to the group of patients.

Supplemental oxygen was delivered at 2 mL/min to spontaneously breathing children via a non-rebreather mask. The children were placed in a supine or prone position according to the location of the urinary tract stone after achieving a Wisconsin sedation score of 1 or 2. All patients received 90 shocks per minute at 18 kV using the PCK Stonelith system (PCK Electronic Industry and Trade CO, Ankara, Turkey). Oxygen saturation and heart rate were monitored continuously and recorded at 5-min intervals throughout the anaesthesia. Each anaesthesia record included the duration of the procedure, additional sedation

required and the total amount of propofol–ketamine consumption.

Sedation and analgesia was considered satisfactory when ESWL was not disturbed by patient movement. Inadequate sedation was defined as difficulty in completing the procedure due to the child's anxiety or inability to remain motionless. The occurrence of procedural and delayed adverse events, such as nausea, vomiting, agitation, hiccup, hypoxia, occurrence of failed sedation and the total time in the ESWL room, were also recorded. If evidence of airway obstruction was present, supplemental airway manoeuvring, including tactile stimulus, chin lift, airway placement, and assist ventilation with a bag and mask system or intubation of the trachea, was established.

After completion of the ESWL, the child was transferred to the recovery room located in the same area. The children were continuously assessed in the recovery room by an observer who was also blinded to group assignment. Recovery time was defined as the time from completion of the ESWL until achievement of a recovery score of 8 as assessed by the Modified Aldrete Scoring (Appendix 2). Children were discharged home when their vital signs had returned to baseline, their level of consciousness was close to baseline and they could maintain a patent airway. Recovery time and adverse effects during the procedure were recorded.

Statistics

Data analysis was performed using SPSS (ver. 11.0; SPSS, Chicago, IL). The primary outcome parameter of this study was propofol–ketamine consumption during the ESWL procedure to maintain patients at a Wisconsin sedation level of 1 or 2. A power analysis indicated that 29 patients per group were required to detect a true difference of 10 mg between groups where the anticipated standard deviation was 13.3. The standard deviation was based on a pilot group of patients undergoing ESWL. The type I error was set at 0.05 and the type II error at 0.20. Categorical data were analyzed by the chi-square test. Statistical tests included the independent samples *t* test for between-group comparisons where the number and distribution of data required parametric tests. Data were presented as means with standard deviation (SD), and a p value of <0.05 was considered to be significant for all comparisons.

Results

Although the adequate number of patients according to the calculated power of the study was 58, a total of 60 patients were studied to compensate for possible exclusion from the study. The patients were comparable in age, sex, weight, height and ASA physical status (Table 1). The duration of the procedure was comparable between groups (Group I, 29. 2 ± 10.8 min; Group II, 27.8 ± 11 min).

The mean propofol–ketamine consumption for each drug was 25.2 ± 17.7 mg in Group I and 35.4 ± 20.1 mg in Group II, with consumption being significantly lower in Group I ($p = 0.04$). The mean propofol/ketamine consumption per body weight for each drug was 1.7 ± 0.9 mg in Group I and 2.6 ± 1.3 mg in Group II and was also significantly lower in Group I ($p = 0.004$). The recovery period was also significantly shorter in Group I (Group I, 19.4 ± 7.9 min; Group II, 29.6 ± 11.4 min; $p < 0.0001$) (Table 2). The haemodynamic variables recorded within 5-min intervals and adverse effects during the procedure were comparable between groups (Figs. 1, 2).

Spontaneous respiration was maintained in all patients in both groups, and no ventilation support was required. Transient oxygen desaturation (<95%) occurred in two patients in Group I and in three patients in Group II immediately after administration of the initial sedation doses and responded to tactile stimulation. Nausea and vomiting was not observed in either of the groups.

Table 1 Patient characteristics

Patient characteristics	Group I ($n = 30$)	Group II ($n = 30$)	p
Age (months)	45 ± 27.7	44.5 ± 36.2	>0.05
Weight (kg)	14.5 ± 4.5	14.6 ± 7.2	>0.05
Sex (F/M) (*n*)	10/20	11/19	>0.05
ASA physical status (I/II) (*n*)	14/16	13/16	>0.05

Unless indicated otherwise, data are expressed as the mean ± standard deviation (SD)

F Female, *M* male, *ASA* American Society of Anesthesiologists

Table 2 Duration of the procedure, propofol–ketamine consumption, propofol/ketamine consumption per body weight and recovery time

Study parameters	Group I ($n = 30$)	Group II ($n = 30$)	p
Duration of the procedure (min)	29.2 ± 10.8	27.8 ± 11	>0.05
Propofol–ketamine consumption (mg)	25.2 ± 17.7	35.4 ± 20.1	0.04
Propofol/ketamine consumption per body weight (mg/kg)	1.7 ± 0.9	2.6 ± 1.3	0.004
Recovery time (min)	19.4 ± 7.9	29.6 ± 11.4	0.0001

Data are expressed as the mean ± SD

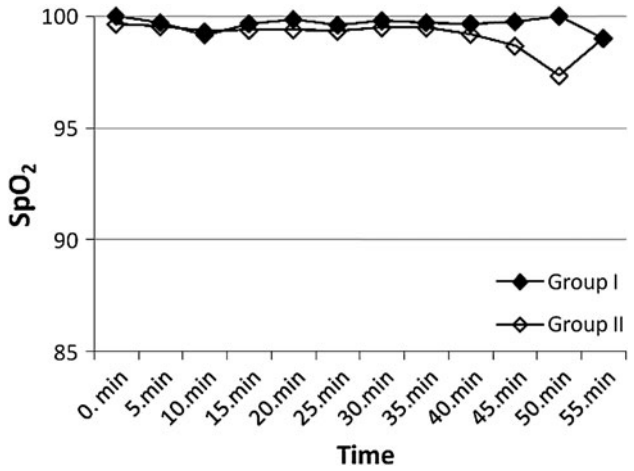

Fig. 1 Mean oxygen saturation (SpO_2) variables of paediatric patients during the electroshock wave lithotripsy (ESWL) procedure

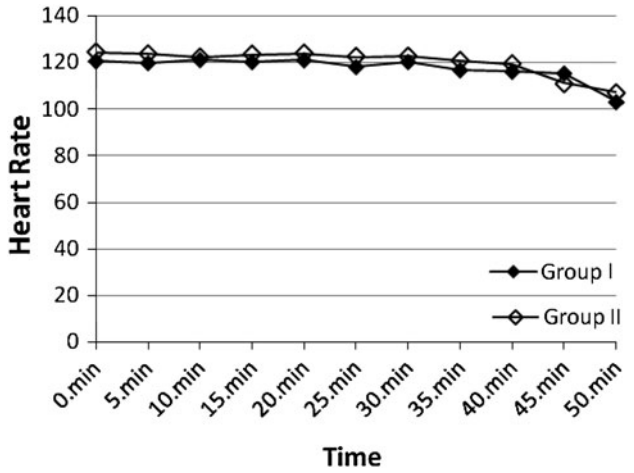

Fig. 2 Mean heart rate variables of paediatric patients during the ESWL procedure

Discussion

The number of therapeutic and diagnostic paediatric interventions performed outside of the operating room setting has increased considerably in recent years. Most of these interventions can be adequately performed with sedation protocols only, with analgesia regimens being required in addition to sedation protocols only in the more painful procedures, such as ESWL. Apart from patient-related factors, ESWL procedure requires selectivity in performing analgesic regimens. A 12% complication rate in 458 paediatric cases was reported in one study, which also found that the procedure could not be completed in 2.4% of these cases and that the most frequently observed complications were hypotension and hypoxemia [8].

For painful procedures, the use of a propofol–ketamine regimen has gained popularity as this combination has been shown to provide adequate sedation levels while maintaining patient safety [9–12]. The pharmacological properties of propofol make it an extremely well-suited hypnotic agent for use in sedation and anaesthesia procedures. The main advantages of propofol in addition to its antiemetic effect are its ability to achieve a deep state of sedation both rapidly and safely and to provide a smooth and quick recovery, as well as its relatively short duration. However, there is a higher frequency of airway problems and consequent falls in saturation values with propofol, and the cardiovascular depressant effects are higher; consequently, propofol must be carefully titrated, especially in paediatric patients [3, 13].

The potential advantages of adding ketamine to propofol therapy include excellent sedation and analgesia in painful procedures with less respiratory assistance and haemodynamic instability [14]. The effect of propofol alone and of the propofol–ketamine combination on respiration has been compared in previous studies; in the propofol group the rate of desaturation was 11.4% and incidence of apnea 17.1%, while these complications were not observed in the propofol–ketamine group [9, 15]. In another study, pain scores and analgesic consumption were found to be significantly lower in the propofol–ketamine group compared with propofol alone [15]. All of these effects at deep sedation levels with low doses are due to the high potency of each agent, and the safety profile is mediated primarily by non-competitive antagonism of reciprocal adverse affects.

There is a considerable heterogeneity in the dosing regimens of the propofol–ketamine combination, but published evidence supports the use of propofol and ketamine in the same syringe for painful procedures. Consequently, we preferred to use this combination in the painful ESWL procedures in paediatric patients. It is also possible that a non-opioid analgesic with a wide safety profile and high tolerability be added on the propofol–ketamine combination to reduce sedative consumption and shorten the recovery time. For this purpose, paracetamol is a widely used analgesic agent in the paediatric patient population.

Paracetamol is a centrally acting inhibitor of cyclooxygenases, and its analgesic mechanism also interacts with the serotonergic system [16, 17]. It is an effective and very well-tolerated analgesic which is only rarely associated with hypersensitivity reactions and lacks the adverse effects of non-steroidal anti-inflammatory drugs or opioids [7, 17, 18]. These properties make paracetamol the preferable choice in our paediatric patients undergoing the ESWL procedure, and our study results demonstrate that the IV administration of paracetamol resulted in a significant reduction in propofol–ketamine consumption with rapid recovery.

In a randomized prospective study involving paediatric ESWL patients, Kaygusuz et al. compared the recovery

time of patients administered only ketamine or only propofol and found recovery time to be significantly longer in the ketamine group (38.9 ± 19.1 vs. 19.2 ± 11.3 min) [19]. The recovery time for the propofol–ketamine combination was 29.6 ± 11.4 min in our study, which is significantly shorter than that for ketamine and significantly longer than that for propofol reported by Kaygusuz et al. [19]. However, the paracetamol add-on regimen reduced our recovery time to 19.4 ± 7.9 min, which is very similar to the propofol recovery time reported by these authors.

The major limitation of our study may be that the conscious level was measured using observational scoring scales instead of monitoring the bispectral index (BIS). Although significant results were demonstrated with a real-life methodology, exhaustive results for propofol–ketamine consumption and recovery times would be achieved with evidence-based follow-up monitoring parameters.

In conclusion, propofol–ketamine combinations may be administered with an ideal safety and comfort profile in paediatric patients undergoing painful procedures, such as ESWL. We have demonstrated that an add-on regimen with a non-opioid analgesic—in our case, paracetamol—significantly reduced propofol–ketamine consumption during the painful ESWL procedure and shortened the recovery time in this group of paediatric patients.

Conflict of interest None.

Appendix 1

See Table 3.

Table 3 The Children's Hospital of Wisconsin Sedation Scale

Sedation classification	Sedation score	Description
Inadequate	6	Anxious, agitated, or in pain
Conscious: minimal	5	Spontaneously awake without stimulus
Conscious: moderate	4	Drowsy, eyes open or closed, but easily arouses to consciousness with verbal stimulus
Conscious: moderate–deep	3	Arouses to consciousness with moderate tactile or loud verbal stimulus
Deep	2	Arouses slowly to consciousness with sustained painful stimulus
	1	Arouses, but not to consciousness, with painful stimulus
Anesthesia	0	Unresponsive to painful stimulus

Appendix 2

See Table 4

Table 4 Modified Aldrete Scoring

Parameter	Description of parameter	Score
Activity	Able to move four extremities voluntarily on command	2
	Able to move two extremities voluntarily on command	1
	Able to move no extremities voluntarily on command	0
Respiration	Able to breathe deeply and cough freely	2
	Dyspnea or limited breathing	1
	Apneic	0
Circulation	BP ±20% of pre-anesthetic level	2
	BP ±20–49% of pre-anesthetic level	1
	BP ±50% of pre-anesthetic level	0
Pulse rate	Pulse ±20 beats of pre-sedation rate	2
	Pulse ±50–21 beats of pre-sedation rate	1
	Pulse >±51 beats of pre-sedation rate	0
Consciousness	Fully awake	2
	Arousal on calling	1
	Not responding	0
O_2 saturation	Maintains baseline saturation on room air	2
	Needs O_2 to maintain >90% saturation	1
	O_2 saturation <90% with O_2 supplement	0

BP Blood pressure

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