Comparison of propofol/fentanyl and ketamine anesthesia in children during extracorporeal shockwave lithotripsy

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ABSTRACT

Objectives: Extracorporeal Shockwave Lithotripsy (ESWL) is an effective and safe way for treatment of upper urinary system stones. For pediatric patients, throughout ESWL, sufficient sedation and analgesia is needed to cope with the procedural pain. In this study, our goal was to compare 2 methods of intravenous anesthesia, applied to pediatric patients during ESWL.

Methods: Forty patients, between 3 months and 15 years of age who were admitted to the Faculty of Medicine, Hacettepe University, Turkey between September 2003 to September 2004 with upper urinary system calculi were randomized into 2 groups. All patients received intranasal midazolam 0.3 mg/kg premedication. Group K received intravenous (iv) ketamine 2 mg/kg; Group PF received a bolus of iv propofol 3 mg/kg and iv fentanyl 1 μg/kg along with a propofol infusion of 1 mg/kg/hr throughout the procedure. Procedural, recovery and discharge times, incidences of intra and post-procedural complications were compared.

Results: Demographics, procedural and discharge times were similar in 2 groups. While recovery times and post-procedural complication incidence was higher for the Group K, intra-procedural complication incidence was higher for the Group PF.

Conclusion: Although both protocols do not differ much according to ease of application and efficacy in providing sufficient analgesia for ESWL, they have their corresponding side effects and they can only be practiced safely by experienced anesthesiologists in a monitorized and well equipped setting.

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Extracorporeal shock wave lithotripsy (ESWL) is the first choice of treatment for most urinary calculi.[1] It has a well established usage in adults and it has been shown to be efficacious and safe, for the treatment of upper urinary tract stones in pediatric patients, with no signs of damage to the growing kidney in long term follow up.[2] Although it requires minimal to no sedation/analgesia in adults, it is difficult for the pediatric patients to cope with the procedural pain or cooperate with the procedure. For the anesthetic management of pediatric ESWL patients, different techniques of anesthesia/analgesia, such as general anesthesia with tracheal intubation, dissociative anesthesia with intravenous (iv) ketamine and patient controlled analgesia usage with alfentanil, have been used, all with acceptable results.[3] We chose to compare ketamine with propofol. Because ketamine which provides rapid onset of deep sedation and analgesia with minimal respiratory depression and cardiovascular side effects[4] also has been used in non-operating room settings such as emergency department,[5] critical care,[6] and radiology suite,[7] settings in pediatrics and propofol has rapid sedative-hypnotic activity and induction and recovery times are generally fast, and the depth of anesthesia can readily be titrated.[4] In this study, our aim was to compare 2 different anesthetic methods during ESWL in children, according to their effectiveness, tolerability and safety.

Methods. This prospective, randomized study included ASA I-II 20 patients in each group (total 40 patients), between 3 months and 15 years of age, who were admitted to the Faculty of Medicine, Hacettepe University, Turkey between September 2003 to September 2004 presenting for ESWL of the upper urinary system calculi. For ESWL procedures Multimed

2001 Elmed Lithotripsy, USA, was used. A power of 99% was calculated for 40 patients, with a 95% confidence interval, according to recovery times and procedural complications. The study was approved by our institutional review board and a written informed consent was obtained from parents of all children, included in the study. Prior to premedication, all patients were evaluated by review of their past and current medical histories, previous experiences of anesthesia and allergic reactions of any kind, a detailed physical examination and a review of laboratory studies. Patients with hemodynamic instability, airway problems, and history of prior adverse reactions to study drugs, increased risk of aspiration, active infection of any kind, increased intracranial pressure and history of seizures were not enrolled into the study. Fasting was required for all patients. Monitors included continuous electrocardiogram (ECG) and pulse oximetry and intermittent (every 5 minutes) non-invasive blood pressure measurements. With the induction and achievement of satisfactory sedation, the urinary calculi were localized and ESWL was started. Anesthesia course and study parameters were recorded. All patients received intranasal midazolam 0.3 mg/kg premedication, 20 minutes before the entry of the iv line and they were randomized into 2 groups, according to the day the patients enrolled. Pediatric ESWL was scheduled for only one day in a week (Wednesday) in our institute so, this method provided reliable randomization. Patients were assigned to propofol/fentanyl (PF) group on odd days and ketamine (K) group on even days. Group K received a bolus of iv atropine 0.01 mg/kg and iv ketamine 2 mg/kg, before the start of the procedure. Group PF received iv propofol 3 mg/kg and iv fentanyl 1µg/kg with induction and an infusion of propofol 1 mg/kg/hr was continued throughout the procedure. For evaluation of sedation levels of the patients, Modified Ramsay Scale was used.[8] A score of 5/6 was aimed for the procedure and lower scores required addition of extra doses of either ketamine or propofol. Intravenous ketamine 1 mg/kg was added, if required, for the Group K; and iv propofol infusion rate was increased to 2 mg/kg/hr, if required, for the Group PF. Any complications, related to induction of sedation, maintenance and early recovery (apnea-cessation of respiration >15 seconds, desaturation - a decrease in SpO_2 <95%, jaw thrust, need of O_2, bag and mask ventilation, tracheal intubation, hypersalivation - an increase in oral secretions which required suctioning by the caregiver, hemodynamic instability - an increase or decrease in blood pressure of 20%, brady-tachycardia, nightmares-hallucinations, seizures, need of extra medication) were noted. Oxygen was administered with

desaturation and bag and mask ventilation was applied at SpO_2 <90%. At the end of the procedure, following recovery, the patients were transferred to the recovery room, with ECG and pulse-oximetry. We provided a dark, quiet environment in the recovery room so that the patients would not be distracted by external stimuli; important, especially, for Group K. The patients were discharged to the ward or their home, as they met our discharge criteria: Alert and oriented patient, with stable vital signs, able to ambulate without help and tolerate clear fluids without nausea and vomiting. Both groups were evaluated for procedural time (PT), recovery time (RT), discharge time (DT); and complications during the procedure and recovery period. Procedural time was defined as time between the start and end of the procedure; RT as, time between the first application of the anesthetic drug and the patient's spontaneous eye opening or appropriate verbal responses or crying, as we have projected procedural times to be similar in all patients as one group received the anesthetic drug as a single bolus (K) and the other as continuous infusion (PF); DT as, time between the end of the procedure and the patient's meeting of our discharge criteria. Patients were not followed up after the discharge.

For the statistical analysis of the data, Statistical Package for Social Sciences 12.0 for Windows was used. Chi-square tests and Kolmogorov-Smirnov tests were used for the evaluation of the patient demographics. Students t-test was used for the evaluation of the procedural, recovery and discharge times, intra and post-procedural complications. A p value <0.05 was accepted as statistically significant.

Results. Forty children, presenting for ESWL of the upper urinary system calculi, were included in the study. There were 20 patients in both groups: 25 boys and 15 girls. Mean age was 6.2±4.4 years and the mean weight of the patients was 21.9±12.1 kg. Patient demographics were similar in 2 groups. None of the patients in either group have experienced failure of sedation and all procedures were performed successfully. Overall, 19 patients in Group PF (95%) and 7 patients in Group K (35%) experienced intraoperative complications. This was statistically significant (*p*<0.01, Students t-test). For Group PF, the most common complication was desaturation, seen in 17 patients (85%), which resulted in need of O_2 supplement and bag and mask ventilation for 15 patients (75%). Apnea was seen in 5 patients (25%); no patient required endotracheal intubation. One patient experienced laryngospasm (5%) and one patient (5%) had bradycardia. Six patients (30%) needed increased dosage of propofol infusion, as their sedation scores were <5. For Group K, although

the most common intraprocedural complication was desaturation, seen in 5 patients (25%), only O_2 administration was enough. Three patients (15%) had hypersalivation and needed suctioning of the secretions. Four patients (20%) needed extra dosage of ketamine, all due to increased procedural time. During the post-procedural period, while 5 patients in Group K (25%) showed adverse reactions, none of the patients in Group PF experienced any complications. This was statistically significant (*p*=0.019, 2-tailed test). Three patients (15%) had nausea and vomiting, one (5%) experienced hallucinations and one (5%) showed agitation, but needed no medication. Procedural times were similar in 2 groups. Recovery times for Group K were longer than that of Group PF. Discharge times were similar (**Table 1**).

Discussion. In the present study, we have evaluated the efficacy, tolerability and safety of 2 anesthetic techniques with intravenous ketamine and propofol/fentanyl for children, during ESWL. The main reason for our broad age range (3 months-16 years) was to determine a standard anesthesia protocol for all the pediatric patients, presenting to our institute for ESWL so, patients of all ages, suitable for our study criteria were included in the study. As Ugur et al[3] have reported, different anesthetic approaches (general anesthesia with tracheal intubation using inhalation anesthetics, dissociative anesthesia with ketamine, conventional analgesia using iv opioids, total iv anesthesia with propofol) have been used during pediatric ESWL procedures, with no particular advantage over each other. The midazolam premedication had its advantages for the pediatric age group: making the iv access easier for us and reducing the anxiety of the patients due to separation from their parents. When ketamine is administered alone, there is a high incidence of delirium and unpleasant dreams during the recovery period.[9] The addition of midazolam to ketamine has been reported to reduce psychotomimetic manifestations effectively during and after emergence from ketamine anesthesia[9] or sedation;[10] but there is still little evidence in children to suggest that midazolam actually has this effect and reduction of anxiety may prove the major benefit of this short-acting benzodiazepine. Sherwin[11] has reported that concurrent midazolam did not diminish agitation due to ketamine and had no measurably beneficial effect, so usage of adjunctive benzodiazepines in pediatric ketamine sedation appeared to be unnecessary. Our low incidence of hallucinations (one patient) may be due to our midazolam premedication. Ketamine and midazolam combination, as a premedication for pediatric patients undergoing ambulatory procedures, under halothane

Table 1 - Procedural time, recovery time, discharge time.

Parameters	Groups (mean±SD)	
	Group K	**Group PF**
Procedural time	15.6±3.6	17.9±5.8
Recovery time	38.9±19.1*	19.2±11.3
Discharge time	55.3±30.2	42.9±20.7
* *P*<0.05, compared with group PF		

anesthesia was shown to prolong recovery and discharge times to unacceptable levels.[12] In our study, recovery times were significantly longer for Group K but, there was not a statistically significant difference between discharge times. Also, we did not have a control group of only ketamine, without midazolam premedication so, we can not reach such a conclusion of prolonged RT or DT, just because of midazolam premedication.

Intraprocedural complications were higher in the Group PF. Desaturation was seen in 17 (85%) patients and apnea, requiring short-term bag and mask ventilation occurred in 15 (75%) patients in Group PF. This is higher than the reports in other studies. Hertzog et al[13] have reported that 13% of their patients experienced respiratory depression under propofol sedation. Vardi et al[6] reported that ratio as 17%. The high rate of respiratory depression in our study was, most probably, due to adjunctive fentanyl and high induction doses of propofol. When the study was first planned, propofol doses were foreseen as 1 mg/kg bolus and 1 mg/kg/hr as iv infusion for maintenance of sedation. But, in our prestudy cases, we observed that these propofol doses were not enough for ESWL procedures in children; so, we had to increase our propofol dosage to 3 mg/kg for induction, along with adjunctive fentanyl 1 µg/kg. However, the relatively low infusion dosage of propofol was sufficient for most patients and only 6 patients (30%) needed increased propofol infusion rate. As a result, our intraprocedural respiratory complications increased in Group PF. Although respiratory depression, desaturation and need for bag and mask ventilation were the most common adverse effects in this group, none of the patients required endotracheal intubation and mechanical ventilation.

In Group K, respiratory depression rates were low; desaturation was seen in 5 patients (25%), with no need for bag and mask ventilation and O_2 administration alone being sufficient. Again, Vardi et al[6] has reported that, in his study of 98 children and 105 procedures, only one patient required endotracheal intubation and short term bag and mask ventilation was needed for 3 patients during ketamine-fentanyl-midazolam sedation.

Parker et al[14] have reported that 1.1% of patients experienced a significant drop in saturation, requiring interruption of the procedure and/or stimulation to improve respiratory effort with a ketamine/midazolam sedation protocol. Slonim and Ognibene[15] has reported a complication rate of 3% with ketamine/midazolam for pediatric procedures. The low incidence of respiratory complications in other studies may be associated with different routes of administration; like intramuscular,[16] or rectal.[17] Green and Johnson[18] stated that rapid iv administration of ketamine may cause central apnea. Our rapid iv bolus of ketamine might have caused the relatively high incidence of desaturation. Cases of transient laryngospasm have been reported and are often associated with hypersalivation or active respiratory infection.[18] The former reaction can be prevented by concurrent administration of atropine, and patients with active infections were excluded from our study. Fortunately, laryngospasm, requiring airway intervention in healthy children is extraordinarily rare; in one study, only 2 children in more than 11589 administrations have been reported to require intubation.[18]

The most frequent post-procedural complication in Group K was vomiting, seen in 5 patients (15%); hallucinations in one patient (5%) and agitation in one patient (5%). The 15% nausea and vomiting rate during the recovery period was comparable to other studies (0-43%).[5,14] Deng et al[10] have stated that the incidence of vomiting because of ketamine (20%) was increased with the ketamine dosage. In Wathen et al's[19] study, laryngospasm and oxygen desaturation incidence was found to be higher in ketamine-midazolam group than ketamine group. They reported that the incidence of significant emergence phenomena was not affected by the addition of midazolam to ketamine.

In the study of Dachs et al,[5] the patients fully established the criteria for discharge in roughly 25 minutes after iv ketamine 1.5 mg/kg administration. Our discharge times were longer, as our ketamine dose was higher (2 mg/kg) and its combination with midazolam premedication also prolonged this duration, as have been reported previously.[12] Seigler et al[20] directly compared propofol and ketamine sedation protocols and found the former to be somewhat superior to ketamine with regard to the shorter time the patients had to stay in a monitored environment.

In our study, midazolam premedication with ketamine and propofol/fentanyl provided efficacious sedation and analgesia during ESWL in children. Although midazolam-ketamine combination is useful in uncooperative children, scheduled for long surgical procedures, it showed prolonged recovery times and this combination of drugs may not be appropriate in a busy ambulatory setting. The propofol/fentanyl protocol provided shorter recovery times, but not without a high incidence of intraprocedural respiratory complications. It is important to bear in mind that in our study, both sedation protocols, although effective and easily applied, proved to have a relatively high frequency of significant side effects and should, therefore, only be used in a monitored environment where experienced anesthesiologists and equipment are readily available for intervention and support of airway or hemodynamic emergencies.

References

1. Lingeman EJ, Lifshitz DA, Evan AP. Surgical management of urinary lithiasis. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ, editors. Campbell's Urology. 8th ed. Philadelphia: Saunders; 2002. p. 3361-3451.
2. Brinkmann OA, Griehl A, Kuwetrtz-Bröking E, Bulla M, Hertle L. Extracorporeal shock wave lithotripsy in children. *Eur Urol* 2001; 39: 591-597.
3. Ugur G, Erhan E, Kocabas S, Ozyar B. Anaesthetic/analgesic management of extracorporeal shock wave lithotripsy in paediatric patients. *Paediatr Anaesth* 2003; 13: 83-87.
4. Reves JG, Glass PSA, Lubarsky DA, McEvoy MD. Intravenous nonopioid anesthetics. In: Miller RD, editor. Miller's Anesthesia 6th ed. USA: Elsevier Churchill Livingstone; 2005. p. 317-378.
5. Dachs RJ, Innes GM. Intravenous ketamine sedation for pediatric patients in the emergency department. *Ann Emerg Med* 1997; 29: 146-150.
6. Vardi A, Salem Y, Padeh S, Paret G, Barzilay Z. Is propofol safe for procedural sedation in children? A prospective evaluation of propofol versus ketamine in pediatric critical care. *Crit Care Med* 2002; 30:1231-1236.
7. Cotsen MR, Donaldson JS, Uejima T, Morello FP. Efficacy of ketamine hydrochloride sedation in children for interventional radiologic procedures. *AJR Am J Roentgenol* 1997; 169: 1019-1022.
8. Meyer S, Aliani S, Graf N, Reinhard H, Gottschling S. Sedation with midazolam and ketamine for invasive procedures in children with malignancies and hematological disorders. *Pediatr Hematol Oncol* 2003; 20: 291-301.
9. Cartwright PD, Pingel SM. Midazolam and diazepam in ketamine anesthesia. *Anaesthesia* 1984; 39: 439-442.
10. Deng XM, Xiao WJ, Luo MP, Tang GZ, Zu KL. The use of midazolam and small dose ketamine for sedation and analgesia during local anesthesia. *Anesth Analg* 2001; 93: 1174-1177.
11. Sherwin TS, Green SM, Khan A, Chapman DS, Dannenberg B. Does adjunctive midazolam reduce recovery agitation after ketamine sedation for pediatric procedures? A randomized, double-blind, placebo-controlled trial. *Ann Emerg Med* 2000; 35: 229-238.
12. Verghese ST, Hannallah RS, Patel RI, Patel KM. Ketamine and midazolam is an inappropriate preinduction combination in uncooperative children undergoing brief ambulatory procedures. *Paediatr Anaesth* 2003; 13: 228-232.
13. Hertzog JH, Dalton HJ, Anderson BD, Shad AT, Gootenberg JE, Hauser GJ. Prospective evaluation of propofol anesthesia in the pediatric intensive care unit for elective oncology procedures in ambulatory and hospitalized children. *Pediatrics* 2000; 106: 742-747.

14. Parker RI, Mahan RA, Giugliano D, Parker MM. Efficacy and safety of intravenous midazolam and ketamine as sedation for therapeutic and diagnostic procedures in children. *Pediatrics* 1997; 99: 427-431.

15. Slonim AD, Ognibene FP. Sedation for pediatric procedures, using ketamine and midazolam, in a primarily adult intensive care unit: A retrospective evaluation. *Crit Care Med* 1998; 26: 1900-1904.

16. Green SM, Nakamura R, Johnson NE. Ketamine sedation for pediatric procedures: part 1, a prospective series. *Ann Emerg Med* 1990; 19: 1024-1037.

17. Holm-Knudsen R, Nygard E, Laub M. Rectal induction of anaesthesia in children. A comparison between ketamine-midazolam and halothane for induction and maintenance of anaesthesia. *Acta Anaesthesiol Scand* 1989; 33: 518-521.

18. Green SM, Johnson NE. Ketamine sedation for pediatric procedures: part 2, review and implications. *Ann Emerg Med* 1990; 19: 1033-1046.

19. Wathen JE, Roback MG, Mackenzie T, Bothner JP. Does midazolam alter the clinical effects of intravenous ketamine sedation in children? A double-blind, randomized, controlled, emergency department trial. *Ann Emerg Med* 2000; 36: 579-588.

20. Seigler RS, Avant MG, Gwyn DR, Lynch AL, Golding EM, Blackhurst W, et al. A comparison of propofol and ketamine/ midazolam for intravenous sedation of children. *Pediatr Crit Care Med* 2001; 2: 20-23.