IJKD KIDNEY DISEASES

Comparison of Propofol-Fentanyl with Midazolam-Ketamine Combination in Pediatric Patients Undergoing Kidney Biopsy

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Introduction. Kidney biopsy is a procedure of choice for the diagnosis of many kidney diseases. In children it is performed with the use of sedatives. The aim of this study was to compare the combination of propofol/fentanyl with midazolam/ketamine for sedation in pediatric patients undergoing kidney biopsy.
Methods. In this double-blinded clinical trial, seventeen children, candidate of kidney biopsy were included and randomized into two groups. One group received Midazolam/Ketamine with doses of 30 to 50 µg/kg and 0.25 to 1 mg/kg, and the other group were sedated with propofol/fentanyl combination in doses of 0.5 to 1 mg/kg and 0.5 to 1 mg/kg, respectively. Administration time, medication doses, total procedure time, need for analgesic use after the procedure, and patient relaxation, with no agitation during and after the biopsy were recorded.
Results. Nine patients received midazolam/ketamine and eight received propofol/fentanyl. None of them experienced vomiting or itching after sedation. There were no meaningful differences in qualitative variables of the need for pain relief between two groups. Regarding the distribution of pain at the time of sedation, and 1, 3, 6, and 24 hours after sedation, there was no significant statistical difference between the two groups. There was also no significant statistical difference between the two groups, regarding patients' relaxation during, and 1, 3, 6, and 24 hours after biopsy.
Conclusion. There was no statistically significant difference between the degree of sedation and the analgesic effect of the two regimens in the two groups.

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Original Paper

INTRODUCTION

Kidney biopsy is the procedure of choice for diagnosis of many kidney diseases, which is almost always performed with sedation in pediatric patients.[1] In pediatric patient care, sedation is provided with the use of propofol and ketamine, due to their safety in outpatient setting.[2,3] The rapid onset of action and clearance, lack of emetogenic properties (especially with propofol), preservation of spontaneous ventilation and appropriate analgesia, at doses used for adequate hypnosis, makes them good options for sedation in this age group.[1] Despite its safety, propofol, at usual doses used for most painful procedures, results in loss of consciousness, while its sedative properties are not adequate, and so, a higher dose of the drug is required for induction of deep sedation. Therefore, the use of propofol is confined to conditions in which trained personnel, in airway management are available.[4] Agents that are used for sedation

and analgesia such as ketamine or propofol, alone or in combination with other medications, such as midazolam and fentanyl, have several side effects including nausea, vomiting, respiratory depression and itching. Opioids are recently used for sedation and general anesthesia, which result in a better painless state and provide more stable cardiovascular state. Therefore, opioids can be used in combination with propofol, to provide better analgesia in patients undergoing painful procedures.

For pediatric patients, ketamine is widely administrated by anesthesiologists. Ketamine provides adequate analgesia and amnesia and deep sedation, at the same time maintains upper airway patency, airway reflexes and respiratory mechanics.[4] It is a potent analgesic with lower risk of respiratory depression as compared with propofol. Midazolam is used in combination with ketamine to reduce its side effects; i.e. anxiety and behavioral non-compliance.[5]

MATERIALS AND METHODS

Seventeen children, who were candidates for undergoing a kidney biopsy under sedation, were enrolled in this prospective double-blind study, and were randomly randomized. with random number method, into two groups (A and B). The patients' age ranged between 4 and 16 years old. An informed consent was obtained from the parents or legal guardians, and written assent was also obtained from children older than seven years, after explanation of the study rationale. The exclusion criteria were contraindications to the use ketamine, analgesics consumption in the past 24 hours, history of allergy to any of the medications, and unwillingness to participate in the study. None of the patients met the exclusion criteria.

All children were examined by a pediatric nephrologist, at the night before the procedure. Patients were ordered to fast, for at least 12 hours before the intervention. They were monitored for blood pressure, pulse rate, and pulse oximetry and electrocardiographic studies were performed before and during the biopsy. A registered nurse, who was not involved in the evaluation of the sedation status of the patients or in the biopsy procedure, was attributed to prepare the medications, in-coded and labelled syringes. The envelopes, containing the case medications, were also labelled, accordingly. Group A received Midazolam/Ketamine at doses of 30 to 50 µg/kg and 0.25 to 1 mg/kg, respectively and group B received Propofol/Fentanyl at doses of 0.5 to 1 mg/kg and 0.5 to 1 mg/kg, respectively. The anesthesiologist administered the sedatives and monitored all patients during the procedure. Administration time, medication doses and total procedure time were recorded. At the end of the biopsy procedure and also after ensuring the return of sufficient spontaneous respiration and airway reflexes, the patients received six liters/minute of oxygen with a facial mask and oxygen saturation and heart rate were monitored with the use of pulse oximetry and electrocardiography.

The Wong-Baker score is a rating scale, which was used to assess pain in our study (Figure).[6] It has a rating score ranging from zero, which is absolute painlessness, to five, that implies severe painful state, and uses patient's facial grimace for the evaluation of pain. In this study if the score was equal to, or greater than four, the patient was given oral acetaminophen as analgesic. The standard Riker Sedation-Agitation Scale was also used to assess agitation of the patients during the biopsy, and one, three and six hours after the procedure (Table 1).[7] Data were collected and analyzed with SPSS version 16 software. The significance level for all statistical tests was .05. The one-sample Kolmogorov–Smirnov test was used to determine whether data were normally distributed. For parametric variables, a *t*-test on two independent samples and for nonparametric variables, the Mann–Whitney *U*-test was used to compare the two groups. Blood pressure and heart rate values were analyzed using repeated measures ANOVA. To compare categorical variables between two groups, Pearson's chi-square versus Fisher's exact test was used. Unless noted otherwise, data were presented as mean ± standard deviation (SD). The study was approved by ethics committee of Mashhad University of Medical Sciences at 2015.01.09 with the approval code: "911040" and is registered in

Wong-Baker Score

Table 1. Riker Sedation-Agitation Scale

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staffs
+3	Very Agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staffs
+2	Agitated	Frequent non-purposeful movements or patient–ventilator asynchrony
+1	Restless	Anxious or apprehensive, but movements are not aggressive or vigorous
0	Alert and Calm	
-1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
-2	Light Sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
-3	Moderate Sedation	Any movement, but no eye contact to voice
-4	Deep Sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

the Iranian Registry of Clinical Trials with the registration number of" IRCT201610247892N5".

RESULTS

We evaluated 17 patients which were randomly divided in two groups, nine patients received midazolam/ketamine and eight received propofol/fentanyl. At first, Kolmogorov–Smirnov test was used to evaluate the distribution of quantitative data variables, and found a normal distribution of all quantitative variables in both groups ($P > .05$). Then by using Levene's test, the variance equality was studied in the two groups. To compare the quantitative variables between the two groups, independent t-test was used considering the normal distribution, same variance, and the significance level of .05. Demographic characteristics including sex, age, height, and other variables such as initial pulse rate and O2 saturation were compared between the two groups (Tables 2 and 3). The two groups did not differ statistically in the abovementioned data.

Nausea and vomiting were evaluated after biopsy and none of the patients of neither groups vomited after sedation. No itching was also reported, during, 1, 3, 6, and 24 hours after biopsy. Two patients, both belonging to group B (11.20%), needed acetaminophen as analgesic.

Table 3. Gender of Participants in the Study

	Group B (%)	Group A (%)	All Patients (%)	*P*
Male	75	44.4	58.8	> .05
Female	25	55.6	41.2	

According to the results of Chi-square and Fisher tests, there was not a significant difference in the need for analgesics between the two groups ($P = .22$). Regarding the distribution of pain and patients' relaxation at the time of sedation and 1, 3, 6, and 24 hours after sedation, there was no significant statistical difference between the two groups (Table 4 and 5, respectively).

DISCUSSION

Kidney biopsy in children is a painful and semi-invasive procedure, and its success and side effects of this procedure depends on the patient cooperation to stay motionless during the biopsy; hence for the achievement of this goal., several sedation methods have been studied. Although many biopsies have been performed with an effective local anesthesia, general anesthesia is sometimes needed in uncooperative children.[8]

Presently a wide variety of sedative drugs are used in children undergoing minor surgical procedures. Midazolam, ketamine, propofol and

Table 2. The initial Characteristics of the Participants in the Study

Variable	Group B		Group A		ALL Patients		*P*
	SD	Mean	SD	Mean	SD	Mean	
Weight, kg	32.87	14.47	33	18.54	32.49	16.23	> .05
Age, y	9.18	4.01	9.33	4.58	9.26	4.19	> .05
Height, cm	125.5	26.47	129.44	28.76	127	26.91	> .05
The First Time Requires Pain Relief	0.87	2.1	0	0	0.41	1.46	> .05
Heart Rate	105.125	28.47	107.66	22.16	106.47	24.53	> .05
O_2 Saturation, %	94.62	5.09	96	2.29	106.47	24.53	> .05

Table 4. Distribution of Pain Between Two Groups

Time	Severity of Pain	Group B (%)	Group A (%)	*P*
During Kidney Biopsy	No	50	33.3	
	Mild	50	44.4	
	Moderate	0	11.1	> .05
	Sever	0	11.1	
	Very Sever	0	0	
1 Hour After Biopsy	No	75	55.6	
	Mild	12.5	22.2	
	Moderate	12.5	22.2	> .05
	Sever	0	0	
	Very Sever	0	0	
3 Hours After Biopsy	No	100	66.7	
	Mild	0	11.1	
	Moderate	0	22.2	> .05
	Sever	0	0	
	Very Sever	0	0	
6 Hours After Biopsy	No	75	88.9	
	Mild	0	11.1	
	Moderate	0	0	> .05
	Sever	13	0	
	Very Sever	13	0	
24 Hours After Biopsy	No	100	88.9	
	Mild	0	11.1	
	Moderate	0	0	> .05
	Sever	0	0	
	Very Sever	0	0	

Table 5. Severity of Agitation Between Two Groups

Time	Severity	Group B (%)	Group A (%)	*P*
During Kidney Biopsy	Calm	12.5	11.1	
	Restless	50	66.7	> .05
	Agitated	38	22.2	
1 Hour After Biopsy	Calm	0	11.1	
	Restless	62.5	77.8	> .05
	Agitated	37.5	11.1	
3 Hours After Biopsy	Calm	0	11.1	
	Restless	63	77.8	> .05
	Agitated	38	11.1	
6 Hours After Biopsy	Calm	0	11.1	
	Restless	63	66.7	> .05
	Agitated	38	22.2	
24 Hours After Biopsy	Calm	0	11.1	
	Restless	63	66.7	> .05
	Agitated	38	22.2	

fentanyl are among the most commonly used medications.[9,10] Using sedatives at the start of kidney biopsy, with the presence of an anesthesiologist to control the patient status, helps the nephrologist to focus more on the procedure. Currently, different drugs are used for sedation before biopsy, and the anesthesiologist' choice depends on the patient's condition, age, presence of underlying diseases and the duration of the procedure. For a long time, safety and efficacy of propofol [11] and ketamine[12] to sedate children has been proved to be acceptable. The aim of this study was to compare the pain reduction and relaxation effects of the two different regimens, midazolam/ketamine and propofol/fentanyl, during the kidney biopsy in children.

A similar study that compared the effect of

midazolam/ketamine and propofol/fentanyl in a minor orthopedic surgery, was performed in a pediatric emergency department by Godambe SA *et al.*, which included 113 patients, aged between 3 to 18 years old.[13] They prescribed each drug as bolus dose, and children's agitation was evaluated using six parameters: 1) patient agitation, as assessed by an independent blinded observer, after videotape review using the OSBD-r (Observational Scale of behavioral Distress-revised); 2) orthopedic satisfaction score (Likert scale 1-5); 3) sedation nurse satisfaction score (Likert 1-5); 4) parental perception of procedural pain defined as: 0 to 100 mm Visual Analog Scale, with the upper limit being "most pain"; 5) patient recall of the procedure ; and 6) 1 to 3 week follow-up. Recovery time in propofol group was clearly less than the ketamine group, agitation was equal in both groups, while there was greater potential for developing respiratory depression and airway obstruction in patients who received propofol.[13]

Although orthopedic procedures are known to be among the most painful procedures, propofol and ketamine equally decreased the pain and distress. However, patients' pain intensity and the need for analgesics was significantly lower in ketamine group than the other group. In this study, the need for analgesics after kidney biopsy was studied in two groups and there was no significant difference. Our results were different from the results of the study by Jeevan Singh',which compared the duration of painlessness, the efficacy of painlessness and the need for analgesics between three regimens; i.e., Ropivacaine, Ropivacaine/ketamine and Ropivacaine/fentanyl in children undergoing a herniorrhaphy surgery.[14]

In our study, pain was investigated during the biopsy, and 1, 3, 6, and 24 hours after the biopsy by the Wong-Baker score and no significant difference was found between the two groups. Our findings were against the results of the study by Jayaram Lee's[15] which compared two groups of children in orthopaedic emergency department, prospectively.[15] They used two drugs combinations: midazolam/ketamine and etomidate/fentanyl for sedation in children who needed fracture fixation. In that study, they evaluated the severity of pain, patient's distress, duration of sedation and recovery and the side effects, and found that the pain score in midazolam/ketamine group was less than etomidate/fentanyl. They also reported that, the midazolam/ketamine combination was more effective for sedation in orthopaedic procedures in the emergency setting, with less pain, distress, and side effects. Etomidate/fentanyl seemed to be a better option for the procedures in which a short-term sedation was needed, as the duration of sedation and recovery was reported to be shorter than the other group.

In another study, performed in 2017, the efficacy and safety of midazolam/ketamine and propofol/fentanyl combinations were compared in children undergoing upper gastrointestinal endoscopy . This randomized single blinded study recruited 238 children (119 patients in midazolam/ketamine and 119 in propofol/fentanyl group). The effectiveness, side effects and recovery period of the two groups were recorded. Twenty- seven (22.7%) patients in the midazolam/ketamine group, and 41 patients (34.5%) in the propofol/fentanyl group showed complications during the procedure, which was significantly higher in the latter group Interestingly, the complication rate during the recovery period was significantly higher in the midazolam/ketamine group. Their study showed that endoscopic procedures can be performed by the midazolam/ketamine combination, but the adverse effects of ketamine during the recovery should be considered.[16]

In our study, the standard SAS (Riker Sedation-Agitation Scale) was used to assess agitation in patients during the biopsy, and one, three and six hours after the procedure, which did not show any difference between the two groups. However, a prospective study by Symington and Thakore in 2003, compared the sedative property of the propofol/fentanyl and midazolam/ketamine regimens in minor orthopedic procedures in pediatric emergency department.[17] They showed that the recovery time and total sedation time were significantly lower in the propofol/fentanyl than in the midazolam/ketamine group, and there was a significant difference between oxygen saturation and late side effects between the two groups. They also reported that the rate of agitation in the propofol/fentanyl group was significantly higher than midazolam/ketamine group. Propofol is associated with more respiratory suppression than ketamine. In our study, the group who received propofol had a higher mean oxygen saturation, however, the difference was not statistically significant. The presence of itching sensation during and 1, 3, 6,

and 24 hours after biopsy and vomiting were also compared between the two groups and no significant difference was found. Our finding was different from the results of the study done by Cha *et al*.[18] They conducted a study on the analgesic effect of low dose ketamine added to fentanyl on patients undergoing chest deformity surgery Patients were randomly divided into two groups, one of which only received fentanyl before and at the end of the operation, and the other one got fentanyl in combination with ketamine. They found that the level of pain, necessitating ketorolac administration, and the amount of fentanyl used were significantly lower in the ketamine group compared to the other group. Adding ketamine to fentanyl also reduced nausea and vomiting without increasing side effects.

CONCLUSION

In conclusion, there was no statistically significant difference between the degree of sedation and the analgesic effect of the two regimens between the two groups, However, since propofol has been proved to have a shorter duration of sedation and faster recovery time, propofol/fentanyl is now the preferred regimen for sedation, and is commonly used for kidney biopsy in children.

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