Original Article

Comparison of the Efficacy of Propofol TCI and Midazolam for Patients undergoing ESWL: A Randomized Controlled Trial

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Background: ESWL is a standard treatment for kidney and ureteric calculi. At Rajavithi Hospital, monitored anesthetic care (MAC) is utilized for this procedure, but patient movement occasionally occurs. Propofol TCI is an alternative technique that helps to maintain patient position and also decrease the total dose of fentanyl used.

Objective: To study the efficacy of propofol TCI compared with midazolam in patients undergoing ESWL for kidney or proximal ureteric calculi.

Materials and Methods: A total of 140 patients who underwent ESWL were randomized into 2 groups. Patients in group 1 received midazolam 0.05 mg/kg intravenously while those in group 2 were given propofol TCI at plasma concentration 1.2 mcg/ml, and doses were adjusted to maintain a sedation score of 4. Both groups received intravenous fentanyl 1 mcg/kg to relief pain, and fentanyl 25 mcg intravenously was added if pain score was greater than 4 or if the patients could not tolerate the pain. The primary outcome was a stone-free rate at 1 month after procedure and secondary endpoints were to compare patient movement, total dose of fentanyl used, time to discharge, and patient and technician satisfaction in the two groups.

Results: The stone-free rate was 56.9% in group 2 (Propofol TCI) and 50.7% in group 1 (Midazolam) (p = 0.477). Patient and technician levels of satisfaction in group 2 were higher than in group 1 (p<0.001 and p<0.001, respectively). In group 1, the total dose of fentanyl used was higher than in group 2 (p<0.001).

Conclusion: The stone-free rate was higher in patients who received propofol TCI than in those who were given midazolam, but the differences were not statistically significant. Patient and technician satisfaction in the propofol TCI group were greater than in the midazolam group, and this difference was statistically significant.

Keywords: Propofol TCI, Midazolam, ESWL

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ESWL (extracorporeal shock wave lithotripsy) is the minimally-invasive treatment of choice for urinary tract stones, particularly those in the kidney and proximal ureter[1,2]. In order to return the patients to a stone-free condition, several factors need to be considered including the shock wave machine, patient movement, the experience of the technician, and stone size and composition[2,3]. Anesthesia is mandatory for this procedure and plays an important role in achieving the best results[4], not only in terms of pain control but also in preventing patient movement. At the authors' institute, midazolam and fentanyl with monitored anesthetic care (MAC) are used for patients who undergo ESWL, but patient movements occasionally occur with these agents, and nausea and vomiting are commonly observed. To maintain patient position and to reduce the incidence of complications, another technique was considered.

Propofol is the ideal sedative agent for outpatient procedures. Its context-sensitive half-time achieves significant reductions in residual sedation, confusion, motor impairment and amnesia, and it also results in less post-operative nausea and vomiting compared with the short-acting benzodiazepine, midazolam[5]. Propofol TCI, therefore, is a suitable alternative method of sedation and pain control which entails fewer complications[3] and facilitates monitoring of plasma concentration for medication administration purposes.

The authors hypothesized that to improve ESWL outcomes, particularly the stone-free rate, it is vital that patients should remain still, and that they should experience minimal pain. The authors compared the efficacy of the two aforementioned techniques in patients who underwent ESWL for kidney or ureteric stones.

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Materials and Methods

This was a randomized double-blinded controlled trial, and the protocol of this research was reviewed and approved by the ethics committee of Rajavithi Hospital (No. 117/2557). Between October 2014 and May 2015, patients scheduled for ESWL at Rajavithi Hospital who were aged 18 to 60 years and had American Society of Anesthesiologists (ASA) physical status I or II were eligible for inclusion in the study. Those with history of allergies to drugs used in the study or chronic use of analgesic drugs were excluded. A total of 140 patients who met the eligibility criteria were selected to participate in the study. Using computer-generated random numbers and opaque sealed envelopes, patients were randomized into 2 groups with allocation ratios of 1: 1. Acetar was administered via an intravenous 20-gauge catheter for pre-hydration at 10 ml/kg over 30 minutes, after which intravenous fluid was given at a maintenance rate to all patients. Oxygen supplementation was given via oxygen canula 2 liters per minute. A nurse anesthetist who was not involved in the study opened an opaque sealed envelope marked with the group of the patient and prepared the medication. Intravenous lines were covered with black tape so that the patients and technicians were not aware of the drug assignment. In Group 1, midazolam 0.05 mg/kg was given intravenously while in Group 2, propofol TCI was given at a plasma concentration of 1.2 mcg/ml, and the dose was adjusted by 0.2 mcg/ml (minimum target plasma concentration = 0.8 mcg/ml, maximum target plasma concentration = 2 mcg/ml) every 5 minutes[6] to maintain a Ramsay sedation score[7,8] of 4. Infusion was stopped 5 minutes before the end of the procedure. Both groups received initial intravenous fentanyl 1 mcg/kg to relieve pain, and supplementary doses of fentanyl 25 mcg intravenously were given to patients whose behavioral pain score[9] was greater than 4 or whose pain tolerance was low.

All patients underwent ESWL using the third-generation machine, Delta 2, and the procedure was carried out by 2 technicians using a similar protocol. The number of shots was recorded, and the intensity and the rates of shock waves were utilized at similar levels.

Patient demographic data, perioperative anesthetic parameters (SBP, DBP, pulse rate, respiratory rate, oxygen saturation, sedation score, pain score, nausea/vomiting score, and time to discharge), and patient movement were recorded every 5 minutes until the end of the procedure after which patient and technician satisfaction levels and total dose of fentanyl used were noted. If there were intra-operative medication-related complications such as desaturation (SpO_2 <95%), apnea, hypotension (MAP <30% from baseline), or bradycardia (HR <50 bpm), they were recorded together with details of how each condition was managed. In the event of desaturation, oxygen canula flow was increased to 4 LPM. Hypotension was treated by loading intravenous fluid 10 ml/kg over 15 minutes, and if no improvement was observed, intravenous ephedrine 6 mg/dose was administered every 3 minutes (maximum dose = 30 mg). For bradycardia, intravenous atropine 0.5 mg/dose was given and patients whose condition did not improve after this treatment were excluded from the study. After the procedure, all patients were observed at the post-anesthetic care unit until a Postanesthetic Discharge score more than 9 was reached, indicating that the patient could be discharged home, and time to discharge from PACU was recorded.

The primary outcome was a stone-free rate 1 month after the procedure; therefore, all patients underwent plain KUB film 1 month after the procedure, and were classified as either stone-free or with residual stone by an urologist who was not involved in the present study. The secondary endpoints were total dose of fentanyl used, time to discharge from PACU, and patient and technician levels of satisfaction for the procedure (score 1 to 5; 1 = strongly dissatisfied, 2 = dissatisfied, 3 = neutral, 4 = satisfied, 5 = strongly satisfied) were recorded and assessed by a nurse anesthetist who was not aware of the drug assignment.

Sample size calculations were based on those of previous studies, with a 70% stone-free rate 40 days after emergency ESWL[10]. Type II error = 0.2 and type I error = 0.05. The sample size was calculated at 63 patients per group, with an additional 10% of subjects to cater for the projected dropout rate. IBM SPSS Statistic version 22.0 was used to perform all statistical analyses. In statistical analysis, mean, percentage, and median (IQR) were used for descriptive data while Student t-test, Pearson Chi-square/Fisher exact test, Mann-Whitney test and Multivariate analysis were used for inter-group comparisons. Statistical significance was set at p-value <0.05.

Results

Patient recruitment and study flow are shown in Figure 1. Between October 2014 and May 2015, a total of 140 patients underwent ESWL for renal or ureteric calculi. Data collection was completed in 132 cases, with 67 patients in the midazolam group and 65 in the propofol TCI group. Demographic data are shown in Table 1.

Intra-operative anesthetic parameters (SBP, DBP, pulse rate, respiratory rate, sedation score, pain score, nausea/vomiting score), and patient movement showed no statistically significant difference in the two groups, as shown in Table 2; however, heart rate and mean arterial pressure were lower in the propofol TCI group than in the MAC group, as shown in Figure 2.

Patient and technician satisfaction levels reported for the propofol TCI group were higher than those of the midazolam group (p<0.001 and p<0.001 respectively), as displayed in Table 3. The median Likert score for propofol TCI was 5 from the patients and 4 from the technicians while the midazolam group received a score of 4 from both patients and technicians. The dosage of propofol required to maintain a Ramsey sedation score of 4 was 228.05$\pm$83.13 mg, and the dosage of fentanyl used was lower in the propofol TCI group than in the midazolam one (77.72$\pm$21.23 mcg and 98.96 $\pm$26.36 mcg, respectively, p<0.001, 95% CI 12.983 to 29.497). After the procedure, all patients were admitted to the post-anesthetic care unit (PACU) until they reached a Post-

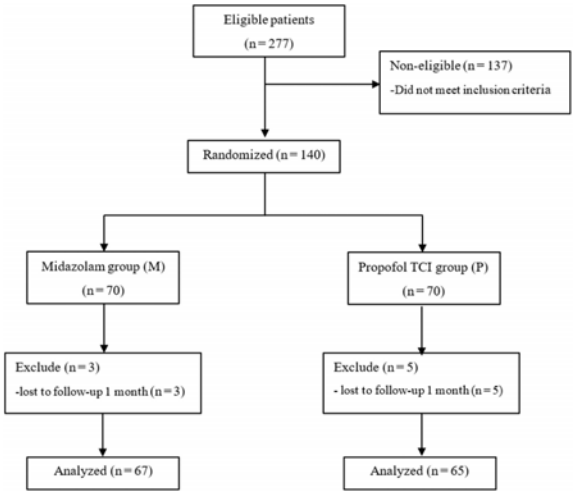


Figure 1. Consort diagram showing the flow of participants through each stage of the randomized trial.

Table 1. Patient demographic data (n = 132)

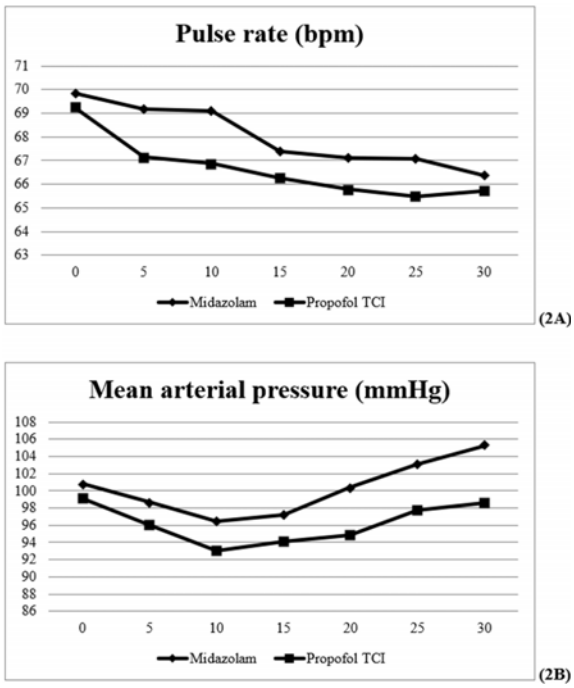
Demographic factors	Midazolam (n = 67)	Propofol TCI (n = 65)
Sex		
Male	39 (58.2)	34 (52.3)
Female	28 (41.8)	31 (47.7)
BMI (kg/m^2)	20.4±3.4	19.8±3.2
Stone location		
Renal calculi	51 (76.11)	49 (75.4)
Ureteric calculi	16 (23.88)	16 (24.6)
Stone size (mm)		
Width	10.5±5.6	10.0±5.0
Length	8.6±4.7	8.1±4.5
Anesthetic time (min)	61.12±13.79	64.23±12.03
Operation time (min)	49.16±13.53	51.92±13.09
Shot (times)	4,423±1,233.50	4,352±1,150.15

Values are presented as n (%) and Mean ± SD

Table 2. Patient movement during the procedure

Patient movement	Midazolam (n = 67)	Propofol (n = 65)	*p*-value
At 0 min	32 (47.8)	27 (41.5)	0.484
At 5 min	17 (25.4)	19 (29.2)	0.511
At 10 min	14 (20.9)	10 (15.4)	0.423
At 15 min	15 (22.4)	18 (27.7)	0.482
At 20 min	20 (29.9)	18 (27.7)	0.784
At 25 min	21 (31.3)	20 (30.8)	0.943
At 30 min	21 (31.3)	22 (33.8)	0.759

Values are presented as n (%). There was no statistically significant difference



The X axis shows the pulse rate, mean arterial pressure and the Y axis shows the operating times at 5-minute intervals. There was no statistically significant difference (*p*-value (2A) = 0.226, *p*-value (2B) = 0.068)

Figure 2. Intraoperative hemodynamic data: 2A displays pulse rates (beats per minute) and 2B shows mean arterial pressure (mmHg) in the MAC (midazolam) group and the Propofol TCI group.

anesthetic Discharge score of 9 points, after which they were allowed to go home. Times to discharge from PACU were recorded and showed that patients who received propofol TCI had a shorter stay than those who received midazolam, but these results were not statistically significant (4.46±17.65 min and 10.52±26.30 min respectively, $p = 0.124$, 95% CI -1.677 to 13.797).

Anesthesia-related complications were recorded during intraoperation and post-operation including oxygen desaturation (SpO_2 <95%), apnea, hypotension, bradycardia, and severe nausea and vomiting. Oxygen desaturation occurred in 7 patients in the midazolam group, and for these patients the flow of oxygen canula was increased to 4 LPM to maintain SpO_2 >95% until the end of the procedure. Post-operative nausea and vomiting was found in 1 patient in the propofol group and 2 patients in the midazolam group ($p = 0.585$). None of the other aforementioned complications was found using either of the techniques.

At the interpretation of the plain KUB film 1 month after the procedure, more patients were stone-free in the propofol TCI group than in the midazolam one, but these results were not statistically significant (56.9% and 50.7%

Table 3. Primary and secondary outcomes

	Midazolam (n = 67)	Propofol (n = 65)	*p*-value	(95% CI)
Technician satisfaction				
Strongly dissatisfied	0 (0.0)	1 (1.5)		
Dissatisfied	1 (1.5)	2 (3.1)		
Neutral	14 (20.9)	8 (12.3)		
Satisfied	38 (56.7)	25 (38.5)		
Strongly satisfied	14 (20.9)	29 (44.6)		
Median (IQR)	4 (4 to 4)	4 (4 to 5)	<0.001*	
Patient satisfaction				
Strongly dissatisfied	0 (0.0)	0 (0.0)		
Dissatisfied	2 (3.0)	0 (0.0)		
Neutral	10 (14.9)	2 (3.1)		
Satisfied	39 (58.2)	14 (21.5)		
Strongly satisfied	16 (23.9)	49 (75.4)		
Median (IQR)	4 (4 to 4)	5 (4.5 to 5)	<0.001*	
Total dose of fentanyl (mcg)	98.96±26.36	77.72±21.23	<0.001*	(12.983 to 29.50)
PACU time (min)	10.52±26.30	4.46±17.65	0.124	(-1.677 to 13.80)
Stone-free rate	34 (50.7)	37 (56.9)	0.477	(-10.80 to 23.15)

Values are presented as n (%), mean ± SD, median (IQR)
95% CI = 95% confidence interval
* = Significant at $p<0.05$

respectively, $p = 0.477$, 95% CI -10.80 to 23.15), as shown in Table 3.

Discussion

ESWL has been accepted as the treatment of choice for kidney and ureteric stones for several decades and anesthesia techniques for this procedure play an important role in achieving the treatment goals. Monitored anesthetic care (MAC) is one of the choices of sedation commonly used during ESWL in many institutes, including the authors' hospital. Patient movement or anxiety can occasionally occur when this technique is employed, and propofol TCI is an alternative modality which can reduce the incidence of these unfavorable events.

This randomized double-blinded controlled trial was performed to compare the effectiveness of midazolam and propofol TCI in ESWL of kidney or proximal ureter stones. There were no statistically significant differences between the demographic data of the patients in the two groups. The stone-free rate achieved was the primary outcome, and this was found to be 56.9% for the propofol TCI group and 50.7% in the midazolam group ($p = 0.477$, 95% CI -10.80 to 23.15). Although the stone-free rate in the propofol TCI group was higher than in the midazolam one, the results were not significantly different.

In evaluating stone-free levels after ESWL, it is important to bear in mind several factors which can have an impact on the outcomes. As reduction of patient movement during the procedure is one of the most important factors in achieving stone-free status, the authors compared the performances of 2 anesthetic agents, propofol and midazolam. In accordance with the ESWL protocol, the stone was fragmented until it disappeared under fluoroscopy or after achieving 4,000 to 6,000 shots. In cases where the patient had moved during the procedure, it was discontinued, and the patient had to be re-positioned properly before undergoing the procedure again; therefore, the stone-free rate was not significantly different in the 2 groups. With regard to the factors which influence stone-free rates, the machine and ESWL protocol used in the present study were comparable, and BMI, number of shots, power of ESWL, and stone location[2,3,10,11] were not significantly different.

Although stone composition was an important factor affecting the outcomes, in the present study, the authors were not able to compare stone composition differences between the patients in these two groups[3,10,12].

Salinas et al[3] reported that one of the factors which influenced analgesic and sedative drug requirements during ESWL was patient anxiety, and the need for analgesic drugs was also influenced by the choice of sedative agent. The present study found that the dosage of fentanyl used was higher in the midazolam group than in the propofol TCI group (98.96±26.36 and 77.72±21.23 mcg respectively, $p<0.001$, 95%CI 12.983 to 29.497). This indicated that pain control during the procedure achieved by propofol TCI was more effective than that obtained using midazolam because of the former's sedative and anxiolytic properties. Patient satisfaction was higher in the propofol TCI group (median = 5 (4.5 to 5)) than in the midazolam one (median = 4 (4 to 4)) ($p<0.001$). Technician satisfaction, assessed from patient co-operation during the procedure, was significantly higher in the propofol TCI group (median = 4 (4 to 5)) than in the midazolam one (median = 4 (4 to 4)) ($p<0.001$).

In the present study, anesthesia-related compli-

cations were not statistically different between the two groups. The patients were able to undergo ESWL and only seven patients had treatable complications (oxygen desaturation); therefore, no patient was excluded from the study.

Stone composition was the major factor affecting achievement of stone-free status after ESWL, and as the authors were unable to perform stone analysis, this was a limitation of the present study.

Conclusion

Patient and technician satisfaction levels were higher in the propofol TCI group than in the MAC one. Stone-free rates were not significantly different in these two groups; however, as mentioned earlier, there were other factors which influenced the achievement of stone-free status. Propofol TCI obtained good results in terms of anxiolytic, pain control, lower fentanyl usage, less post-operative nausea and vomiting, and shorter time to discharge; therefore, especially in the case of anxious patients, the use of propofol TCI should be considered.

What is already known on this topic?

For patients undergoing ESWL, comfort during the operation results from adequate levels of sedation and pain control; therefore, drugs that have faster recovery time and fewer side effects are preferable. Another study has shown that both propofol and dexmedetomidine achieve good sedation and adequate pain control, but propofol often triggers incidences of desaturation, and dexmedetomidine is expensive. Other research has indicated that when propofol and fentanyl are given together, the recovery and time to discharge improved.

What this study adds?

The stone-free rate in ESWL depends on patient movement during the procedure. In both groups, patient movement and also the stone-free rate were not significantly different. However, patient co-operation during the procedure assessed by technician's satisfaction was significantly higher in the propofol TCI group. The patients in the propofol TCI group also had lower anxiety and required less analgesia; thus, the patients in this group had better levels of satisfaction.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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