

A novel triple oral regime provides effective analgesia during extracorporeal shockwave lithotripsy for renal stones

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Abstract

Context: Analgesia during extracorporeal shockwave lithotripsy for renal stone is an essential component. It not only makes the procedure comfortable but also increases the stone-free rate.

Aims: The aim of this study was to evaluate the efficacy of triple oral analgesic agents on stone fragmentation and pain relief in comparison to injectable analgesic agents.

Settings and Design: This prospective randomized study included 68 patients of renal calculi of size 5–15 mm.

Subjects and Methods: Group A had 32 patients, who received injection pentazocine and injection diclofenac, 45 min before the procedure. Group B consisted of 28 patients, who received a combination of oral acetaminophen, 325 mg, oral diclofenac 50 mg, and oral tramadol 37.5 mg, 45 min prior. Procedural findings, pain score visual analog scale (VAS), fragmentation rate, and outcome were recorded.

Statistical Analysis Used: Independent *t*-test and Pearson's correlation test.

Results: A total of 60 patients were analyzed. The mean age was 40.2 ± 11.8 years. Both groups were comparable in body mass index, stone size, number, and density. Group A required more shocks than Group B (4274 vs. 3693, $P = 0.043$). A lower energy level of shocks (kV) was tolerated in Group A (2.5 vs. 3.2, $P = 0.002$). Group A required more sittings than Group B (2.3 vs. 1.9, $P = 0.037$). VAS score was significantly less in Group B (2.9 vs. 4.9, $P = 0.0001$). The overall fragmentation rate was similar among groups (81.2% vs. 89.3%); hence, the successful outcome was (59.4% vs. 75.0%, $P = 0.274$). The occurrence of adverse events was also equivalent in both groups ($P = 0.199$).

Conclusions: Triple oral regime provides better analgesic effect and quicker stone-free rate than injectable agents but with similar final outcome.

Keywords: Calculi, extracorporeal shockwave lithotripsy, kidney, medicine, pain

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INTRODUCTION

Stone disease of urinary tract affects around 8.8% of the population.^[1] Various modalities of treatment are available. Extracorporeal shockwave lithotripsy (ESWL) is an option

of choice for selective small to medium size calculus of kidney and upper ureter. Although it is a least-invasive procedure, multiple sittings and lower stone-free rate

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are the disadvantages. Its overall efficacy varies from 50% to 90%.^[2]

Various factors affect the fragmentation and clearance following ESWL, most important being the stone size, density, location, skin to stone distance, and pelvicalyceal anatomy.^[3] Many other factors also appear to alter the outcome such as respiratory movements, body mass index (BMI), and adjuvant medications; however, their definite role is questionable.^[4-6] One such factor is the choice of analgesic. Historically, general and regional anesthetics were used during ESWL. Newer generation lithotripters are much more safe and tolerable, although at a cost of lower fragmentation ability. A variety of intravenous, intramuscular, local, and oral analgesic combinations have been suggested in the literature.^[7] Despite that, there is no uniform consensus on the type of analgesia and agent used.

We compared the safety and efficacy of triple oral analgesic combination to the injectable analgesic agents in patients undergoing ESWL for renal calculus disease.

SUBJECTS AND METHODS

Study design

The prospective randomized study was conducted in the Department of Urology during the study period from July 2015 to June 2016. Approval of the Institutional Ethical Committee was taken. The sample size was calculated with the help of G * Power software version 3.1.9.2 (Heinrich-Heine-University, Düsseldorf, Germany) after calculating an effect size of 0.6. Alpha error and power were kept at 0.05 and 0.8, respectively. Patients were enrolled after written informed consent. They were divided into two groups. Block randomization method (blocks with equal size of 10) was used using Random Allocation Software Version 1.0.0 (Isfahan University of Medical Sciences, Isfahan, Iran). CONSORT guidelines were followed.

Study protocol

Sixty-eight adult patients of renal calculus of size 5–15 mm were screened. Clinical examination followed by noncontrast computed tomography kidneys, ureters, and bladder (KUB), X-ray KUB, urine culture, serum creatinine, prothrombin time, and INR was done in all the patients. Patients with deranged renal function (estimated glomerular filtration rate <30/ml/min/1.73 m²), coagulopathy (INR >1.5), hard stones (density > +1500 Hounsfield unit [HU]), and altered pelvicalyceal anatomy were excluded from the study. Sterile urine culture was favored. Patients with two subsequent positive urine cultures despite treatment were maintained on antibiotics during ESWL. Routine antibiotic prophylaxis was given in all cases with single dose of tablet levofloxacin, 500 mg, 1 h before ESWL.

Group A patients received a combination of injection pentazocine, 30 mg, IM and injection diclofenac, 75 mg, IM, 45 min before the procedure. In Group B patients, triple oral analgesic regime was utilized. A combination of acetaminophen, 325 mg and tramadol, 37.5 mg (Tab Ultracet, Janssen pharmaceuticals) along with diclofenac, 50 mg (Tab Voveran, Novartis India Ltd) was administered 45 min before the procedure. ESWL was given using Dornier compact sigma under fluoroscopic guidance. Gradual ramping protocols were followed. A maximum of 3000 shocks was allowed in one sitting.

Outcome analysis

Primary endpoints of the study were assessment of pain level during ESWL and the final outcome. The pain was expressed through visual analog scale with a score range of 0–10. The final outcome was measured regarding success or failure. Success was defined by either complete clearance of stone or clinically insignificant residual fragments of <4 mm size, 4 weeks after the session.

Secondary endpoints examined were total number of shocks, number of sittings required, energy level tolerated, fragmentation, and clearance rate. Fragmentation was classified into complete (<4-mm fragments), partial (>4-mm fragments), and no fragmentation. Stone clearance was assessed after 4 weeks with X-ray KUB. Three sittings were given in the presence of persistent residual calculi of more than 4 mm size. Clearance was classified into complete (no residual fragments), partial (clinical insignificant residual fragments <4 mm), and no clearance (>4-mm residual fragments). Adverse events were expressed by modified Clavien-Dindo (MCD) classification.

Statistics applied

Statistical analysis was done with the help of SPSS software, version 21.0 (IBM Corp, NY, USA). Descriptive data were presented in the form of mean, median, percentage, and standard deviation. Independent *t*-test was used for comparison between two groups. The association between categorical variables was examined using Chi-square and Fisher-exact tests. Continuous variables were analyzed through scatter plot and Spearman's rho correlation test. Statistical significance was kept below 0.05, and the confidence interval was selected at 95%.

RESULTS

Baseline characteristics

Sixty cases were finally available for the analysis [Figure 1]. Mean age and BMI of the study patients were

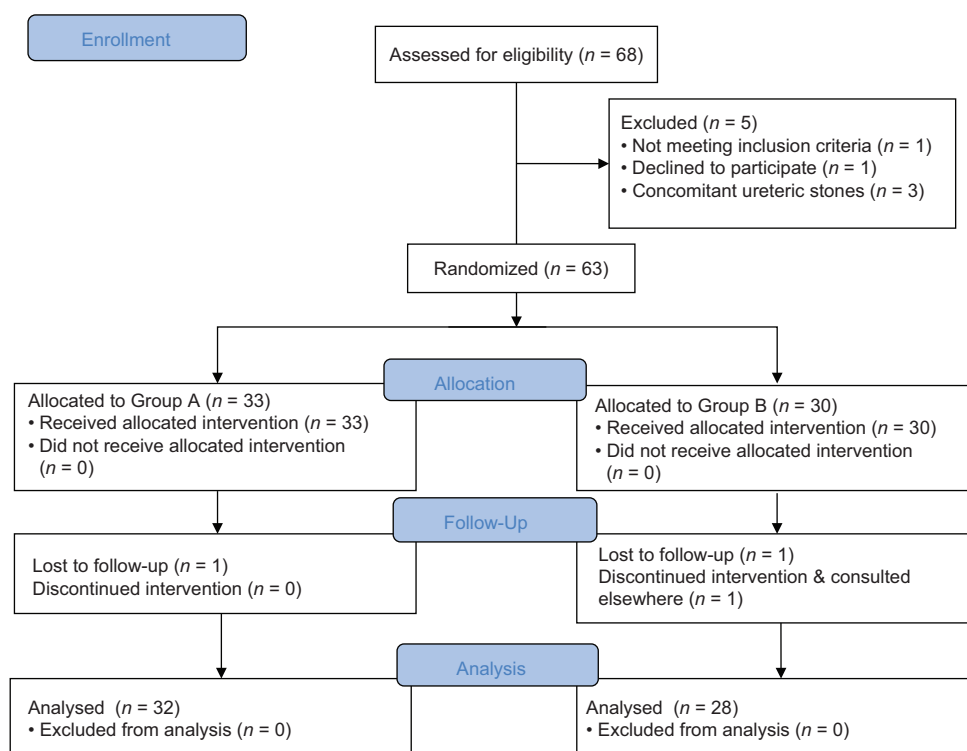


Figure 1: Chart showing the flow of participants enrolled in the study

40.2 ± 11.8 years and 25.7 ± 3.3, respectively. Thirty-four patients were female, and 26 were male. Mean renal stone size was 10.3 ± 2.7 mm. The renal pelvis was the most common location of stones in 35.0% of cases, followed by middle calyx (30.0%), lower calyx (26.7%), and upper calyx (8.3%). Stone density ranged from + 363 to + 1500 HU. Multiple renal stones were found in 23.3% of cases, with bilateral stones in 10% of cases. Groups A and B had 32 and 28 participants, respectively. Both the study groups were comparable in age, BMI, stone size, density, and location [Table 1].

Procedural findings and pain score

Group A required more number of shocks and number of sittings than Group B [Table 2]. A higher energy level of shocks was tolerated by Group B patients. Mean pain score in Group A and B was 4.9 and 2.9, respectively [Table 2]. Two patients in Group A and one in Group B could not tolerate shockwaves even at Level 1, leading to premature termination of session.

Fragmentation, clearance, and outcome

Complete stone fragmentation was observed 12.5% of cases in Group A and 28.6% in Group B. However, partial fragmentation rate was higher in Group A (68.8%) than Group B (60.7%) [Table 2]. Total clearance and CIRF was found in 12.5% and 43.8% of cases in Group A, respectively, while in Group B, it was seen in 21.4% and

Table 1: Baseline clinical and stone parameters in the study groups

Parameters	Group A (n=32)	Group B (n=28)	P
Age (years)	38.7±11.8	42.0±12.0	0.284
Gender (male:Female)	1: 1	1: 1.8	0.305
BMI (kg/m ²)	26.3±2.6	25.0±3.8	0.098
Stone size (mm)	10.8±2.9	9.7±2.4	0.129
Stone density (HU)	930±290	900±302	0.695
Stone location			
L	9.32	7.28	1.0
NL	23.32	21.28	

L: Lower polar, NL: Nonlower polar, BMI: Body mass index

53.6% of cases, respectively. The successful outcome occurred in 59.4% and 75.0% of cases in Groups A and B, respectively.

Adverse events

MCD Grade I complications were observed in 56.3% and 67.9% of cases in follow-up period in Groups A and B, respectively. Majority of these included postprocedure pain, suprapubic discomfort, nausea, and vomiting. They were managed by analgesic and antiemetic medications as prn. Most of the patients required them for single day only. Grade II complications were reported by five study participants [Table 2]. Two patients were treated for urinary tract infection; three patients required alpha-blockers for nonprogression of stone fragments; two patients required temporary ureteric stenting under local anesthesia; and one for persistent renal colic and another for steinstrasse.

DISCUSSION

ESWL is an excellent noninvasive modality for small renal and upper ureteric stones. Current European Association of Urology guidelines recommend it as a first-line option for renal stones of <10 mm size.^[8] Its efficacy, however, decreases to a great extent in larger (>10 mm), lower polar, and harder stones (>1000 HU).^[9] Various conditions influence the final outcome following ESWL. A good analgesia and adequate patient relaxation during the procedure are of utmost important. It not only allows the delivery of high-energy shockwaves but also improves the targeting of stones by lesser body movements.

Various anesthetic and analgesics combinations have been evaluated in recent years [Table 3]. These studies provide a wide array of options for analgesia during ESWL including

intravenous, intramuscular, gel, local infiltration, and oral agents.^[10-16] Their reported efficacy varies a lot among the studies. Our choice of triple oral agents was based on their proven individual efficacy in injectable forms, along with the oral formulation being more comfortable for all patients. In fact, the idea of this mode of therapy came from few past experiences, where patients felt more pain from an injectable agent than from the overall ESWL procedure.

Despite good analgesic effects reported by various studies, they failed to provide an impact on overall outcome. We found a similar fragmentation, clearance rate, and overall outcome in both study groups. However, we also noted a significant decrease in number of shocks delivered and the number of sittings required in oral therapy group, to

Table 2: Comparison of extracorporeal shockwave lithotripsy procedural parameters, pain score, and outcome in the study groups

Parameters	Group A (n=32), n (%)	Group B (n=28), n (%)	P	95% CI of differences	
				Lower	Upper
Number of shocks (mean±SD)	4274±1042	3693±1133	0.043	18	1143
Number of sittings	2.3±0.7	1.9±0.8	0.037	0.03	0.81
Energy level (kV)	2.5±0.8	3.2±0.9	0.002	-1.2	-0.3
Pain score*	4.9±1.9	2.9±1.7	0.000	1.1	2.9
Fragmentation					
Complete	4 (12.4)	8 (28.6)	0.257		
Partial	22 (68.8)	17 (60.7)			
Nil	6 (18.8)	3 (10.7)			
Clearance					
Complete	4 (12.4)	6 (21.4)	0.285		
CIRF**	14 (43.8)	15 (53.6)			
Nil	14 (43.8)	7 (25.0)			
Outcome					
Success	19 (59.4)	21 (75.0)	0.274		
Failure	13 (40.6)	7 (25.0)			
Complications					
Grade I [#]	18 (56.3)	19 (67.9)	0.199		
Grade II	3 (9.4)	2 (7.1)			
Grade IIIa	1 (3.1)	1 (3.6)			
Grade IIIb	0 (0.0)	0 (0.0)			

*Measured by visual analog score (0-10), **Clinical insignificant residual fragments, [#]By modified Clavien-Dindo classification system. CIRF: Clinically insignificant residual fragments, SD: Standard deviation, CI: Confidence interval

Table 3: List of studies evaluating analgesic effect of various agents

Author	Cases	Analgesic type	Result	Comment
Liu and Zang, 2013 ^[10]	105	IM diclofenac, EMLA gel, and diclofenac gel	All are equal, P=1.34	Local reaction with gel occurred
Hanoura et al., 2013 ^[11]	50	Paravertebral block versus local bupivacaine infiltration	Similar VAS in both, better satisfaction and lesser rescue analgesia with block	More time needed to achieve block
Ozkan et al., 2012 ^[12]	95	Injection loroxicam, injection PCM, and injection tramadol	L was better, P<0.05	IV administration needed for all
Akcali et al., 2010 ^[13]	90	Injection loroxicam, injection PCM, and injection tramadol	All are effective	Similar adverse events
Eryildirim et al., 2009 ^[14]	120	EMLA gel, IM diclofenac, and combination	Diclofenac is better, P=0.002	Combination is no superior
Greene et al., 2009 ^[15]	69	Tablet rofecoxib versus control	Less post-ESWL pain with R, P<0.0001	
Bilir et al., 2008 ^[16]	60	Placebo, injection loroxicam, and injection tenoxicam	L provides greater pain relief, P<0.05	Difference in effect was seen only after 45 min
Our study	60	Double IM versus triple oral	Fewer shocks with superior pain relief with T, P=0.0001	Similar outcome

VAS: Visual analog scale, IV: Intravenous, ESWL: Extracorporeal shockwave lithotripsy

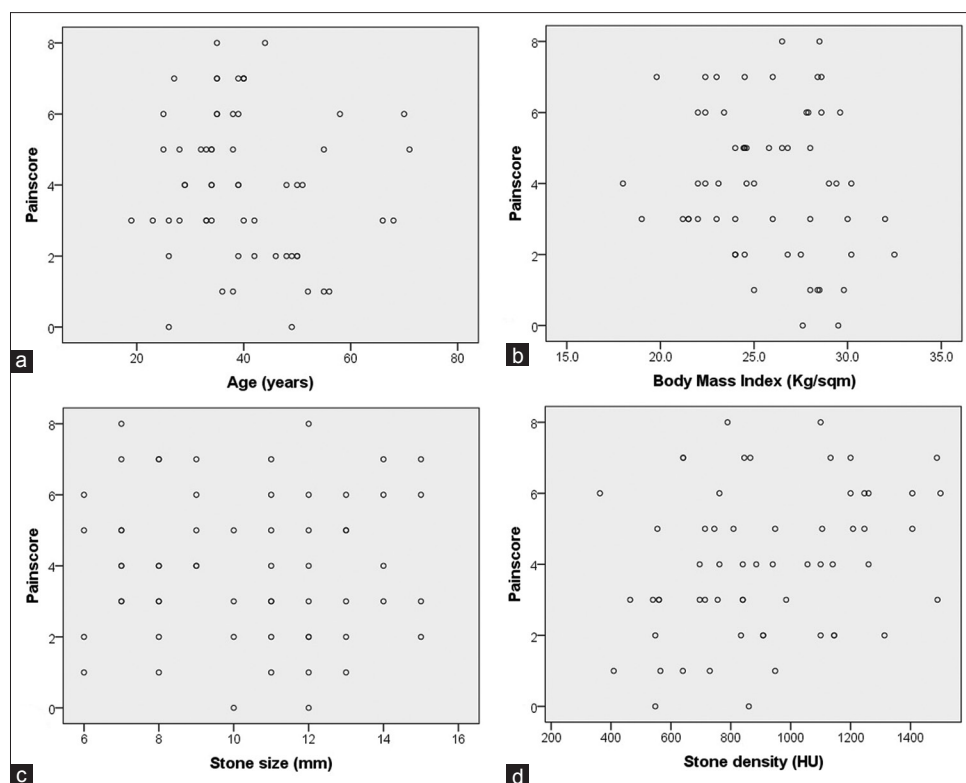


Figure 2: Scatter plot showing the relation of pain score to age (a), body mass index (b), stone size (c), and stone density (d)

achieve a comparable outcome. A higher energy level of shocks could also be tolerated in the same group. These parameters were not examined in the previous reports.

Vergnolles *et al.* studied different predictive factors for pain during ESWL.^[17] He found patients with depression, anxiety, history of prior ESWL, homogenous stones, and of younger age experienced more pain and required greater analgesia. We did not find any correlation of pain score with age ($r = -0.132$), BMI ($r = -0.146$), and stone size ($r = -0.028$), except a weak correlation with stone density ($r = 0.291$) [Figure 2]. Limitation of this study may be the small sample size, lack of placebo control, and comparison of only two combination regimes.

CONCLUSIONS

Patients receiving triple oral regime tolerated the procedure better than their counterparts. Though overall fragmentation and success rate was similar in both groups, triple oral regime group achieved it in lesser number of sittings and with fewer number of high powered shocks.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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