A Prospective, Randomized Study of the Clinical Effects of Shock Wave Delivery for Unilateral Kidney Stones: 60 Versus 120 Shocks per Minute

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Purpose: We assessed the effects of different shock wave delivery rates in patients treated with shock wave lithotripsy for renal stones, particularly treatment success, degree of renal injury and pain experienced, and analgesic demand.

Materials and Methods: A total of 206 patients with renal stones were prospectively randomized to receive shock waves delivered at 60 (group 1) or 120 (group 2) shocks per minute using a Sonolith® Vision at a single institution in October 2008 and August 2010. The primary outcome was successful treatment 12 weeks after 1 lithotripsy session. Secondary outcome measures included the degree of renal injury, as reflected by changes in urinary markers of renal injury, as well as patient pain scores and analgesia consumed during treatment.

Results: Mean stone size in groups 1 and 2 was 8.95 and 9.28 mm, respectively ($p = 0.525$). The overall treatment success rate was 43.2%. It was significantly better in group 1 than in group 2 (50.5% vs 35.9%, $p = 0.035$). There was no between group difference in the success rate for stones 10 mm or less but the success rate was statistically better for group 1 patients with stones greater than 10 mm ($p = 0.002$). Immediately after shock wave lithotripsy there was a statistically significant greater increase in urinary NAG ($p = 0.003$) and interleukin-18 ($p = 0.022$) in group 1. There was no between group difference in pain scores, analgesic consumption during shock wave lithotripsy or unplanned hospital visits.

Conclusions: Slower shock wave delivery yielded better treatment outcomes, particularly for stones greater than 10 mm, without increasing patient pain or analgesic demand. However, slower shock wave delivery also appeared to cause a statistically significant increase in acute renal injury markers, although the clinical implication was uncertain.

Key Words: kidney, kidney calculi, lithotripsy, iatrogenic disease, pain

Abbreviations and Acronyms

CT = computerized tomography

IL-18 = interleukin-18

MSD = mean stone density

NAG = N-acetyl-β-D-glucosaminidase

NCCT = noncontrast computerized tomography

NGAL = neutrophil gelatinase-associated lipocalin

SWL = shock wave lithotripsy

Submitted for publication January 26, 2012.

Study received institutional review board approval.

Supported by Hong Kong Research Grant Council General Research Fund 471508.

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EXTRACORPOREAL SWL remains a recommended first line treatment for renal stones. There have been continuous modifications in its applications meant to further improve treatment outcomes. A recently investigated treatment variable is the shock wave delivery rate. Increasing evidence suggests that a slower delivery rate improves stone clearance.[1] However, we believe that treatment assessment should also include the risk of renal injury and patient tolerance. Animal studies suggest that a slower shock wave delivery rate may produce less renal injury[2] but to our knowledge this has not been ver-

0022-5347/12/1883-0837/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2012.05.009
Vol. 188, 837-842, September 2012
Printed in U.S.A.

ified in clinical studies. Thus, we assessed the effects of different shock wave delivery rates on stone clearance, renal injury and patient perception of pain.

MATERIALS AND METHODS

This was a single center, prospective, randomized study. The study was approved by the institutional ethics review board and done in accordance with good clinical practice guidelines and the Declaration of Helsinki (trial registration ChiCTR-TRC-09000627). All patients provided written informed consent before enrolment.

Patients

Patients 18 years old or older with a solitary 5 to 20 mm renal stone were recruited for study. Patients with multiple stones in the same calyx or a stone associated with any anatomical renal or ureteral abnormality and patients with a ureteral stent/nephrostomy tube were excluded from analysis, as were those with cystinuria or a history of allergy due to alfentanil.

Study Procedures

After background information was obtained NCCT was done with a multidetector row CT scanner to confirm stone presence and size, and measure various stone parameters. A spot urine sample (50 cc) was collected to measure urine markers.

Patients were randomized to SWL at 60 (group 1) or 120 (group 2) shocks per minute. We chose 60 shocks per minute based on an in vitro study showing that this was the most effective shock wave delivery rate.[3] At our center 120 shocks per minute has been used routinely, as commonly used elsewhere.[4–9] All patients were treated with the Sonolith Vision, an electroconductive lithotripter with an aperture of 219 mm, focal distance of 130 mm, maximal focal zone of 25 $\times$ 3.6 mm and peak pressure at a focal point of 92 to 106 MPa.

Patient controlled analgesia was used during treatment. The preset intravenous bolus dose of alfentanil was 40 μg and the lockout period was 1 minute. All treatments were aimed to deliver 1,000 J energy at 14.4 kV, which was the manufacturer recommended maximum energy per treatment session, unless stone localization failed or the patient could not tolerate the procedure.

Upon completion of treatment patients were asked to rate the level of pain verbally on a scale of 0 to 10. Another spot urine sample was collected for marker measurement immediately after treatment.

Followups were performed on days 2 and 7, and weeks 4 and 12. At each followup a spot urine sample was collected and plain x-ray was done for outcome assessment. If patients were considered stone free on x-ray at week 12, NCCT was performed to confirm stone clearance. Further treatment was based on clinical information, residual stone size and patient choice. All re-treatment was done after week 12 unless earlier treatment was indicated.

Urinary Marker Measurement

Spot urine was collected to monitor renal injury markers. The urinary markers assessed included NAG, NGAL and IL-18. NAG was measured with a commercial colorimetric assay kit. NGAL and IL-18 were measured with enzyme-linked immunosorbent assay kits. All marker levels are shown as the ratio with regard to urinary creatinine, which was measured by an automated analyzer. All measurements were made in duplicate and the mean was used for analysis.

Main Outcome Measures

The primary outcome measure was successful treatment, defined as stone-free status or residual fragments less than 4 mm 12 weeks after SWL. Secondary outcome measures included the degree of renal injury, as reflected by changes in urinary marker levels, and patient pain scores, analgesic consumption and complication rates.

Sample Size

The study protocol called for the recruitment of 220 patients. Sample size was calculated based on previous studies by assuming a success rate of 65% for group 1 and 45% for group 2. With these assumptions an estimated 214 patients were needed to provide 80% power with significance at 5% and a 10% dropout rate.

Randomization and Allocation Concealment

All eligible patients were randomly assigned to the 2 groups at a 1:1 ratio. Preset, sequentially numbered envelopes containing paper with group allocations were prepared by a research assistant according to the randomization scheme generated by a website (http://www.randomization.com) with a block size of 2 or 4 and without stratification. Randomization was achieved by the duty urologist drawing an envelope before SWL. Investigators and radiologists who assessed clinical outcomes and the research staff that measured urine markers were blinded to patient treatment information.

Statistical Analysis

Differences between the 2 groups were analyzed statistically. Demographic data were analyzed by the Student t and Mann-Whitney U tests. Categorical variables were analyzed by the chi-square or Fisher exact test. Two-tailed $p < 0.05$ was considered statistically significant.

Outcome analysis was done on an intent to treat basis. Logistic regression was also used to assess the individual effects of various potential predictive factors, including the shock wave delivery rate, on treatment outcome.

Differences in urinary marker levels were analyzed by the Student t test. The mean posttreatment maximum change in urinary markers and the difference in urinary markers after treatment were assessed by the paired t test for normally distributed data and otherwise by the Wilcoxon signed rank test.

Pain scores and analgesic consumption of the 2 groups were compared by the Mann-Whitney U test. Complications were compared by stratified chi-square analysis or the Fisher exact test, when appropriate. Data were analyzed using PASW® Statistics 18.0.

RESULTS

A total of 220 patients fulfilled recruitment criteria and provided consent for the trial in October 2008 and August 2010. Of the patients 14 were excluded from study after consent, including 7 with no renal

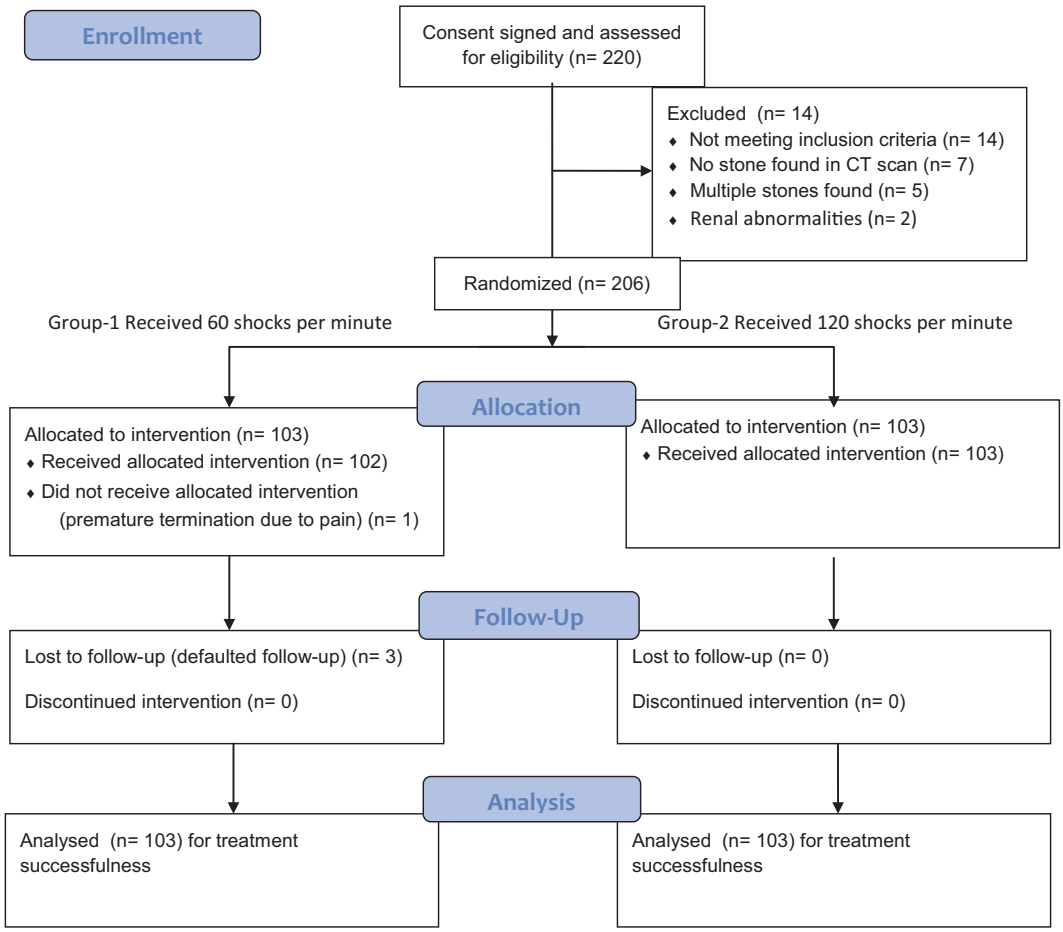

Figure 1. Patient progress through study

stone on NCCT, 5 with multiple stones on NCCT and 2 with renal abnormalities. Thus, 206 patients were randomized to treatment with 103 per group. Groups 1 and 2 included 67 (65.0%) and 64 men (62.1%), respectively ($p = 0.664$). Treatment was terminated prematurely in 1 group 1 patient due to intolerable pain after only 700 shocks. Three group 1 patients were lost to followup. Thus, at 12 weeks 99 and 103 patients were available for followup in groups 1 and 2, respectively (fig. 1).

Patient clinical characteristics and stone parameters were comparable in the groups except more stones were on the left side in group 1 (63 or 61.2% vs 47 or 45.6%, $p = 0.025$). In group 1 vs 2 the stone was in the upper, mid and lower calyx in 13 (12.6%) vs 9 (8.7%), 28 (27.2%) vs 32 (31.1%) and 62 (60.2%) vs 62 cases (60.2%), respectively ($p = 0.608$). Treatment time and total radiation dose were significantly greater in group 1 than in group 2 (table 1). Treatment was terminated prematurely in 5 group 1 and 3

Table 1. *Patient clinical characteristics and treatment related variables*

	Mean ± SD Group 1 (range)	Mean ± SD Group 2 (range)	p Value
Age	55.2 ± 10.5 (25–80)	52.4 ± 11.2 (25–82)	0.064
Body mass index (kg/m^2)	25.3 ± 3.4 (17.9–33.8)	24.4 ± 4.3 (16.2–44.1)	0.083
Stone size (mm)	8.95 (5.00–19.66)	9.28 (5.00–20.00)	0.525
Stone density (HU)	576.1 ± 129.3 (236–831)	569.2 ± 159.5 (268–969)	0.732
Stone vol (cc)	0.34 ± 0.40 (0.2–2.47)	0.35 ± 0.42 (0.04–2.27)	0.814
Total energy (J)	986.7 ± 69.3 (442–1,000)	991.7 ± 59.3 (549–1,000)	0.575
No. shocks	3,310.1 (1,500–3,646)	3,372.2 (1,981–3,594)	0.063
Treatment time (mins)	71.0 ± 13.7 (40–140)	42.5 ± 8.5 (25–70)	<0.001
Radiation dose (mGy/cm^2)	23,684 ± 20,109 (598–105,831)	17,160 ± 15,178 (1,503–75,881)	0.011
Treatment end pain score	4.0 ± 2.2 (0–8)	4.5 ± 2.2 (0–8)	0.071
Analgesic dose (mg)	121.8 ± 156.1 (0–600)	111.8 ± 138.0 (0–680)	0.886

Table 2. *Stone size, treatment outcomes and re-treatment*

	Overall	Group 1	Group 2	p Value
Stone size (mm):				
Mean (range)	9.12 (5.00–20.00)	8.95 (5.00–19.66)	9.28 (5.00–20.00)	0.525
No. 10 or less	139	73	66	0.298
No. greater than 10	67	30	37	
No. treatment success (%):	89 (43.2)	52 (50.5)	37 (35.9)	0.035
Stones 10 mm or less	72 (51.8)	39 (53.4)	33 (50.0)	0.687
Stones greater than 10 mm	17 (25.4)	13 (43.3)	4 (10.8)	0.002
No. re-treatment (%)	88 (42.7)	43 (41.7)	45 (43.7)	0.640
Re-treatment before wk 12:				0.884
No. pts	14	8	6	
Mean wk (range)	7.43 (3–10)	7.25 (3–10)	7.67 (6–10)	
Re-treatment wk 12 or after:				0.755
No. pts	74	35	39	
Mean wk (range)	16.01 (12–57)	16.63 (12–57)	15.46 (12–27)	

group 2 patients since targeted stones became invisible during localization. In groups 1 and 2 a median of 3,382 and 3,383 shocks were given and at treatment end the pain score was 4 (IQR 2–6) and 5 (IQR 3–6), respectively.

The overall treatment success rate was 43.2% (89 patients). It was significantly better in group 1 than in group 2. For stones 10 mm or less the overall treatment success rate was 51.8% and there was no difference between the groups. However, for stones greater than 10 mm the overall treatment success rate was 25.4% and the result was statistically significantly better for group 1 than for group 2 (43.3% vs 10.8%, p = 0.002, table 2).

Logistic regression was performed to further assess the effect of the shock wave delivery rate on treatment outcome. Stone size 10 mm or less, lower MSD and treatment with 60 shocks per minute were significant predictors of overall treatment success (table 3). For patients with stones 10 mm or less only MSD was a significant predictor of successful treatment (table 3). However, for those with stones greater than 10 mm, in addition to stone size and patient age, treatment with 60 shocks per minute was a significant predictor of success (table 3). Other potential predictors analyzed were patient gender, stone side, site and volume, and skin-to-stone distance.

Table 3. *Multivariate analysis of significant predictors of successful treatment*

	Adjusted OR (95% CI)	p Value
Overall:		
Stone size	0.844 (0.753–0.945)	0.003
MSD	0.997 (0.994–0.999)	0.008
MSD stones 10 mm or less (139 pts)	1.985 (1.079–3.653)	0.028
Stones greater than 10 mm (67 pts):		
MSD	0.996 (0.993–0.999)	0.006
60 Shocks/min	6.078 (1.575–23.451)	0.009
Stone size	0.751 (0.574–0.982)	0.036
Age	0.946 (0.885–1.012)	0.104

All 3 urinary markers increased significantly above baseline and peaked immediately after SWL in each group ($p < 0.05$, table 4 and fig. 2). NAG decreased gradually to baseline by week 4 in each group, indicating steady repair of renal tubular tissue. Urinary IL-18 and NGAL decreased to baseline as early as day 2. NAG (p = 0.003) and IL-18 (p = 0.022) were significantly higher in group 1 than in group 2 immediately after SWL (fig. 2, *A* and *B*). However, there was no difference in the 2 markers at other post-SWL time points. There was no statistically significant difference in urinary NGAL at any time during the study (fig. 2, *C*).

There was no statistical difference in end of treatment pain scores, analgesic consumption or the incidence of unplanned hospital visits (tables 1 and table 5). Only 2 patients per group required in hospital treatment (table 5).

Table 4. *Urinary marker levels*

	Mean ± SD Group 1	Mean ± SD Group 2	p Value
NAG (IU/mmole creatinine):			
Before treatment	1.01 ± 2.24	1.12 ± 2.30	Not significant
Immediately after treatment	3.00 ± 2.88	1.66 ± 2.26	0.003
Day 2	1.34 ± 1.40	1.46 ± 2.36	Not significant
Day 7	1.46 ± 1.97	1.10 ± 1.74	Not significant
4 Wks	0.878 ± 1.11	0.840 ± 1.11	Not significant
IL-18 (μg/mole creatinine):			
Before treatment	3.30 ± 2.72	3.67 ± 4.13	Not significant
Immediately after treatment	9.70 ± 10.0	6.23 ± 1.14	0.022
Day 2	2.99 ± 2.58	3.17 ± 2.77	Not significant
Day 7	2.47 ± 2.22	2.96 ± 3.10	Not significant
4 Wks	2.37 ± 1.39	3.16 ± 2.93	Not significant
NGAL (gm/mole creatinine):			Not significant
Before treatment	2.78 ± 5.64	2.96 ± 5.05	
Immediately after treatment	9.50 ± 10.8	9.72 ± 9.29	
Day 2	3.01 ± 5.66	3.04 ± 7.70	
Day 7	1.60 ± 3.43	1.94 ± 3.67	
4 Wks	1.39 ± 2.59	1.74 ± 3.54	

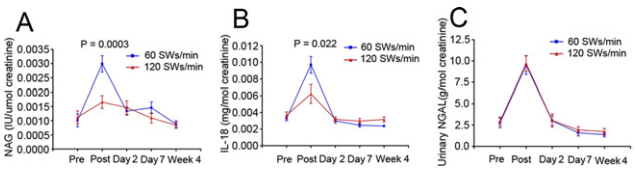

Figure 2. Changes in urinary markers from baseline (*Pre*) to 4 weeks after treatment (*Post*). *A*, NAG. *B*, IL-18. *C*, NGAL.

DISCUSSION

Increased evidence suggests that slower shock wave delivery results in better treatment outcomes.[1,4,5,7] Despite our lower success rates, which may be related to the high percent of lower calyceal stones (greater than 60%), our findings were similar to those in other studies. Univariate and multivariate analyses revealed that the slower rate was a significant factor for treatment success.

The underlying mechanism of this phenomenon is not certain. Wiksell and Kinn proposed that a faster shock wave rate resulted in a shorter pause time for the cavitational bubble cloud to dissolve.[10] The persistent bubble cloud would attenuate the subsequent shock wave and decrease treatment efficacy. However, Pishchalnikov et al suggested that the cavitational bubbles did not persist between shock waves.[11] Instead, the cavitation nuclei carried by fine particles released from stone fragments absorbed part of the energy during the negative pressure phase of the shock wave and decreased the effect of cavitation bubbles on stone fragmentation. Nevertheless, there are also concerns regarding the slower rate, such as prolonged treatment time and increased analgesic demand.[12] Thus, a more comprehensive assessment of the effects of shock wave delivery rate is needed.

In an experimental study by Evan et al juvenile pigs that received shock waves at a slower rate had less surface and parenchymal bleeding.[2] However, few clinical studies have assessed the effect of the shock wave delivery rate on renal injury. Thus, we selected 3 urine markers of renal injury (NAG, NGAL and IL-18) for monitoring. NAG is a lysosomal enzyme present abundantly in proximal renal tubular cells that has been extensively used to assess tubular injury in SWL related series.[13–15] Urinary NGAL[16–19] and IL-18[19,20] are newer markers for diagnosing acute renal injury. NGAL is a useful early predictor of acute renal injury in various settings, including ischemia, nephrotoxicity, etc. The increase in NGAL after SWL implied acute renal injury, which may have been related to ischemia or another cause. IL-18 is a marker of acute tubular necrosis and inflammation. We hoped that this combination of traditional and new renal injury markers would provide more comprehensive assessment of renal injury after SWL.

We observed acute increases in all 3 urinary markers immediately after SWL in each group. In group 1 the maximum NAG and IL-18 levels were significantly higher than in group 2. In contrast, changes in NGAL were similar in the groups at all study time points. The clinical significance of these findings is still uncertain.

These observed differences in urine markers were not in accord with a previous animal study showing that more renal injury was associated with faster shock wave delivery.[2] However, differences in study design and methodology might have resulted in the differences in study results. Our clinical study used urine markers to assess renal injury while the animal study used histological assessment. Different assessment tools might reflect different aspects and severity of renal injury. In the animal study there was no stone in the renal system and lower pole localization was based on imaging. In contrast to the in vitro study, the presence of stones might have had some effect on shock wave dynamics, such as cavitation bubble formation, which might have affected the surrounding renal tissue. The lithotripsy machines used in our study and the previous animal study also differed. The different focal size and peak pressure of the machines might also have contributed to the different results.

On the other hand, each study only assessed acute renal injury after SWL. Long-term effects of the shock wave delivery rate, such as new onset hypertension or a change in urine markers of renal fibrosis, were not monitored. Thus, further studies are needed to clarify the acute and long-term effects of the shock wave delivery rate on the kidney. Post-treatment imaging, such as ultrasound,[4] CT or magnetic resonance imaging,[21] may help assess renal injury.

In addition to treatment success and renal injury, we assessed the pain perceived by patients and the analgesic demand during treatment. We initially postulated that prolonged treatment due to the slower rate might lead to more discomfort and greater analgesic consumption. However, there was

Table 5. *Unplanned hospital visits (p = 0.818)*

	Group 1	Group 2	p Value
No. admissions	2	2	1.000
Reason:			
Loin pain	7	10	0.613
Lower urinary tract symptoms	1	6	0.119
Fever/sepsis	3	2	1.000
Gross hematuria	2	2	1.000
Nausea and vomiting	1	2	1.000
Dizziness	0	1	1.000

no significant difference in the end of treatment pain score and the actual analgesics consumed. In a comparison of patients receiving SWL at 60, 90 and 120 shocks per minute those who received 120 shocks per minute had a significantly higher need for additional analgesics/sedatives than the other 2 groups.[7] However, the difference in the analgesic protocol and in the machine type might have affected the pain experienced and the analgesic demand. Thus, direct comparison of these results might be difficult.

In our series patients treated at the slower rate received a significantly greater radiation dose. This was probably related to the staff practice of performing regular fluoroscopic monitoring during treatment. This increase in radiation exposure may be significant, especially for patients who require multiple treatments. Precautions, such as real-time ultrasound monitoring, should be encouraged to minimize radiation exposure during SWL.

A study limitation was that we compared only the effects of 60 and 120 shocks per minute during SWL. We did not assess other shock wave delivery rates, which might have provided a more balanced performance in terms of treatment outcome, renal injury, treatment time, etc. For example, by comparing the results of 60, 90 and 120 shocks per minute during SWL for kidney stones Yilmaz et al concluded that 90 shocks per minute was the optimal frequency for clinical use.[7] Including 90 shocks per minute as a treatment arm in future studies may help determine the best delivery rate for the patient.

CONCLUSIONS

In this prospective, randomized study the slower shock wave delivery rate of 60 shocks per minute provided a better treatment outcome, mainly for renal stones greater than 10 mm in size, without a significant increase in the pain experienced by patients and the analgesic demand. However, slower shock wave delivery was also associated with a more significant transient increase in acute urinary renal injury markers. Thus, slower shock wave delivery should be considered in patients with greater than 10 mm stones but not in patients with smaller stones.

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