

SHOCK WAVE LITHOTRIPSY AT 60 OR 120 SHOCKS PER MINUTE: A RANDOMIZED, DOUBLE-BLIND TRIAL

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ABSTRACT

Purpose: The rate of shock wave administration is a factor in the per shock efficiency of shock wave lithotripsy (SWL). Experimental evidence suggests that decreasing shock wave frequency from 120 shocks per minute results in improved stone fragmentation. To our knowledge this study is the first to examine the effect of decreased shock wave frequency in patients with renal stones.

Materials and Methods: Patients with previously untreated radiopaque stones in the renal collecting system were randomized to SWL at 60 or 120 shocks per minute. They were followed at 2 weeks and 3 months. The primary outcome was the success rate, defined as stone-free status or asymptomatic fragments less than 5 mm 3 months after treatment.

Results: A total of 220 patients were randomized, including 111 to 60 shocks per minute and 109 to 120 shocks per minute. The 2 groups were comparable in regard to age, sex, body mass index, stent status and initial stone area. The success rate was higher for 60 shocks per minute (75% vs 61%, $p = 0.027$). Patients with larger stones (stone area 100 mm² or greater) experienced a greater benefit with treatment at 60 shocks per minute. The success rate was 71% for 60 shocks per minute vs 32% ($p = 0.002$) and the stone-free rate was 60% vs 28% ($p = 0.015$). Repeat SWL was required in 32% of patients treated with 120 shocks per minute vs 18% ($p = 0.018$). Fewer shocks were required with 60 shocks per minute (2,423 vs 2,906, $p < 0.001$) but treatment time was longer (40.6 vs 24.2 minutes, $p < 0.001$). There was a trend toward fewer complications with 60 shocks per minute ($p = 0.079$).

Conclusions: SWL treatment at 60 shocks per minute yields better outcomes than at 120 shocks per minute, particularly for stones 100 mm² or greater, without any increase in morbidity and with an acceptable increase in treatment time.

KEY WORDS: kidney, lithotripsy, kidney calculi, lithiasis

Shock wave lithotripsy (SWL) is the most common first line treatment for the majority of renal stones. However, treatment success rates vary from 60% to 90% depending on stone composition, size and location.¹ Patients with large or hard stones may require multiple SWL treatments or more invasive surgical modalities if SWL fails.²

There are a number of variables that can affect the per shock efficiency of SWL, including lithotriptor design, energy setting, shock wave electrode consumption level and the rate at which shock waves are administered.³ Studies done by our group and others have demonstrated that decreasing shock wave frequency can result in improved stone fragmentation in vitro and in animal models.^{3,4} Knowledge of the precise mechanism of SWL induced stone fragmentation is incomplete. However, a number of theories have been advanced to explain improved fragmentation with decreased SWL frequency, including decreased acoustic impedance mismatch, improved cavitation bubble production on the stone surface and improved bubble dynamics due to water gas content surrounding the stone.⁵

While SWL is noninvasive, shock waves can cause renal injury with an area of intraparenchymal hemorrhage in the

line of the blast path. Complications such as subcapsular and retroperitoneal hemorrhage are well recognized and long-term issues such as hypertension, particularly in older patients, are of concern. These complications arise from damage to the renal parenchyma, which is directly related to the number of shock waves, maximum kV administered⁶ and the rate of voltage escalation during treatment.⁷ If a slower shock wave rate leads to clinically improved stone fragmentation with a fewer total number of shocks, patients could be at decreased risk for these side effects and be spared additional SWL or more invasive surgical treatments.

To our knowledge this study is the first to examine the effect of a slower shock wave frequency (60 shocks per minute) compared with the standard rate of 120 shocks per minute during SWL in patients with renal stones. We hypothesized that while decreasing SWL rate might improve SWL success for all types of stones, there was likely to be a differential benefit depending on stone size. It has been well demonstrated that larger kidney stones have a lower success rate with SWL, while smaller stones are more likely to be fragmented with a single treatment.^{1,8} Therefore, it was our hypothesis that decreasing the rate of SWL would have a greater benefit for larger stones.

MATERIALS AND METHODS

A double-blind, prospective, randomized, controlled trial of SWL at 60 and 120 shocks per minute was performed. The target population included patients with previously untreated, radiopaque renal calculi 5 mm or more in diameter

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Study received institutional research ethics board approval.

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who were candidates for SWL treatment. Patients with multiple stones in the same calix, radiolucent stones, cystine stones, stones located within a caliceal diverticulum, faintly opaque stones that would be difficult to target fluoroscopically, renal anatomical anomalies such as horseshoe kidney, ureteropelvic junction obstruction and infundibular stenosis or medical contraindications to SWL, or patients who were unable to return to the kidney stone center for followup were excluded from study. The study protocol was approved by our institutional research ethics board.

Sample size calculation. The preplanned sample size requirement was based on certain assumptions, that is the estimated success rate would be 72% for 120 shocks per minute⁸ and 85% for 60 shocks per minute,⁹ type I error (α) would be 0.05 (2-tailed), type II error (β) would be 0.2 (power of 80%) and the inflation factor would be 10% for potential withdrawals. This result yielded a projected sample size of 220 patients.

Treatment details. After the provision of informed consent and entry into the trial patients underwent simple block randomization to SWL at a rate of 60 or 120 shocks per minute. Randomization was stratified by stone location (lower calix, renal pelvis and upper/middle calix) and stone size (maximum diameter less than 10 mm and 10 mm or greater). SWL was performed on a LithoTron (HealthTronics, Marietta, Georgia) according to a standardized treatment protocol. Biplanar fluoroscopy was used for stone localization and fluoroscopy was performed at least every 200 shocks to ensure appropriate targeting. Treatment began at an energy setting of 17 kV and increased by 1 kV every 100 shocks to a maximum of 22 kV. All treatments were performed with a new electrode and by 1 of 7 treating urologists with experience with at least 500 SWL treatments. SWL was terminated when the treating urologist and lithotripsy technologist agreed that the stone appeared to be completely fragmented or when 3,000 shocks had been administered. Digital x-ray images of the treated stone were printed before and after each SWL treatment and reviewed by a blinded urologist to ensure appropriate targeting and patient enrollment.

Patients were followed at 2 weeks with plain x-ray of the kidneys, ureters and bladder, and at 3 months with plain x-ray of the kidneys, ureters and bladder, and renal tomography, noncontrast spiral computerized tomography (CT) of the abdomen and pelvis or excretory urography (IVP) with tomography to confirm stone-free status. A blinded urologist ascertained treatment outcome at the 2-week and 3-month visits. Treatment success was defined as stone-free status, adequate fragmentation (asymptomatic renal fragments less than 5 mm) or sand (asymptomatic fragments 2 mm or less) following a single SWL treatment. Repeat SWL was performed for residual fragments 5 mm or larger, for symptomatic fragments of any size or for any obstructing ureteral fragments. All cases that required repeat SWL or ancillary treatments, such as ureteroscopy or percutaneous nephrolithotomy (PCNL), to treat stones were defined as failures. Stone-free status was confirmed with renal tomography in 153 patients, CT in 7, including 6 in the 60 shocks per minute group, and IVP with tomography in 5, including 3 in the 60 shocks per minute group. A total of 54 patients with readily visible fragments on plain x-ray of the kidneys, ureters and bladder did not require more detailed imaging. Renal tomography was chosen over spiral CT to better distinguish between multiple sand-like fragments and a single larger fragment.

Statistical analysis. All analyses were performed with the intent to treat principle with data analyzed according to randomization group. The primary outcome measure was the success rate, which was assessed 3 months after treatment. Success and stone-free rates, and other nonparametric parameters were compared with stratified chi-square analysis and the Mantel-Haenszel statistic or Mann-Whitney test when appropriate. The impact of other variables on treat-

ment success was explored using binary logistic regression. Change in stone area following treatment was compared with repeated measures ANCOVA after assuring the normality of data distribution with Levene's test of homogeneity. Other parametric parameters were compared with the Student t test. Statistically significant differences were considered at 2-sided $p < 0.05$.

RESULTS

Screening for suitable cases began July 2001 and ended September 2003 at the kidney stone center at our institution. A total of 802 potential candidates met inclusion criteria, of whom 174 were excluded for multiple stones in the same calix, 63 for only faintly radiopaque stones, 28 for renal anatomical anomalies (horseshoe kidney and infundibular stenosis), 12 for stones in a caliceal diverticulum, 9 for being enrolled in another SWL trial, 9 for ureteropelvic junction obstruction and 3 for a known history of cystinuria. SWL is a regionalized resource in Canada and, as a result, patients often travel more than 100 km for treatment. A total of 245 patients were excluded after refusing to return to the kidney stone center for followup and 39 eligible patients refused entry into the study. The remaining 220 patients provided informed consent and were enrolled, of whom 111 and 109 were randomized to SWL at 60 and 120 shocks per minute, respectively. One patient per treatment group was lost to followup. These cases were included in statistical analysis and treated as failures. Figure 1 shows a complete patient flow diagram.

Table 1 lists baseline characteristics. The 2 treatment groups were comparable in regard to patient age, sex, body mass index (BMI), stone location and ureteral stent or nephrostomy tube status prior to treatment. Lower caliceal stones represented 110 stones (50%) treated in the trial. There was a trend toward larger stones in the 60 shocks per minute treatment group at baseline.

Aside from the SWL rate SWL treatments were similar in the 2 groups (table 2). In the 60 shocks per minute arm fewer shocks were required to achieve initial stone fragmentation under fluoroscopic guidance (801 vs 1,236, $p < 0.001$) and fewer shocks were required to complete treatment (2,423 vs 2,906, $p < 0.001$). Mean treatment time was longer in the 60 shocks per minute arm (40.6 vs 24.2 minutes, $p < 0.001$). All SWL treatments were completed according to protocol, that is treatments were stopped after 3,000 shocks or when the stone appeared to fragment completely. Electrocardiogram

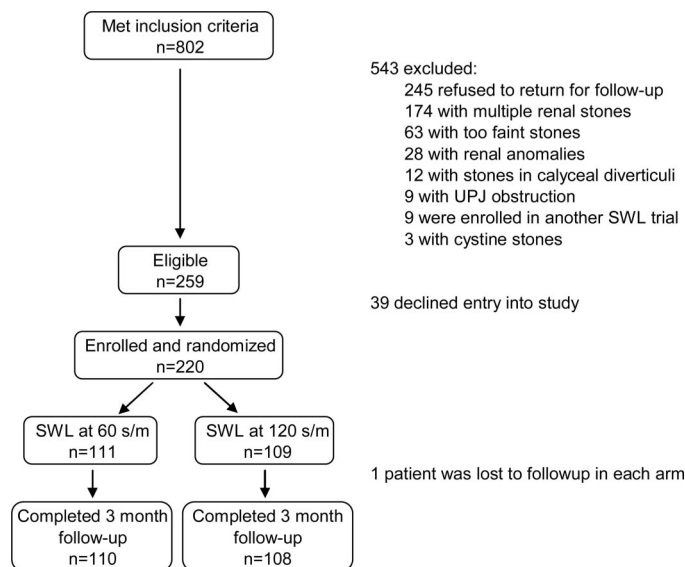


FIG. 1. Patient flow diagram. UPJ, ureteropelvic junction

TABLE 1. Baseline characteristics

	SWL (shocks/min)		Totals
	60	120	
No. pts enrolled (%)	111 (50.5)	109 (49.5)	220
No. sex (%):			
F	53 (47.7)	50 (45.9)	103 (46.8)
M	58 (52.3)	59 (54.1)	107 (53.2)
Mean age \pm SD	49.2 \pm 11.9	50.7 \pm 13.5	49.9 \pm 12.7
Mean BMI \pm SD	27.0 \pm 5.2	27.8 \pm 5.4	27.4 \pm 5.3
Mean initial stone area \pm SD (mm ²)	84.4 \pm 59.4	80.4 \pm 65.7	82.4 \pm 62.5
No. stones less than 100 mm ² (%)	73 (65.8)	84 (77.1)	157 (71.4)
No. stones 100 mm ² or greater (%)	38 (34.2)	25 (22.9)	63 (28.6)
No. pretreatment ureteral stent (%)	23 (20.7)	23 (21.1)	46 (20.9)
No. side (%):			
Lt	60 (54.1)	70 (64.2)	130 (59.1)
Rt	51 (45.9)	39 (35.8)	90 (40.9)
No. location (%):			
Upper calix	13 (11.7)	9 (8.3)	22 (10.0)
Middle calix	9 (8.1)	14 (12.8)	23 (10.5)
Lower calix	58 (52.3)	52 (47.7)	110 (50.0)
Renal pelvis	31 (27.9)	34 (31.2)	65 (29.5)

TABLE 2. SWL treatment data

	SWL (shocks/min)		p Value
	60	120	
Mean max kV \pm SD	22 \pm 0.13	22 \pm 0.30	Not significant
No. kV temporarily decreased due to pt discomfort (%)	6 (5.4)	7 (6.4)	Not significant
Mean fluoroscopy time \pm SD (mins)	4.9 \pm 0.9	4.1 \pm 0.4	Not significant
Mean No. shocks to first fragmentation \pm SD	801 \pm 547	1,236 \pm 633	<0.001
Mean total No. shocks \pm SD	2,423 \pm 730	2,906 \pm 317	<0.001
Mean treatment time \pm SD (mins)	40.6 \pm 12.0	24.2 \pm 11.9	<0.001
No. immediate complications (%):			
Retroperitoneal hematoma	0	0	Not significant
Ventricular bigeminy greater than 1 min	1 (0.9)	3 (2.8)	Not significant
ECG gating required	0	1 (0.9)	Not significant

(ECG) gating of the shock wave generator was required in 1 patient in the 120 shocks per minute arm who had prolonged runs of ventricular tachycardia during treatment. He received the last 1,852 shocks of his treatment at an average rate of 78 shocks per minute and his data were analyzed in the 120 shocks per minute group following the intent to treat principle. There were no clinically significant retroperitoneal hematomas noted and all SWL treatments were done on an outpatient basis.

Table 3 lists SWL treatment outcomes at 2 weeks and 3 months. Success rates were higher in the 60 shocks per minute arm at 2 weeks (79.1% vs 67.0%, $p = 0.043$) and 3

months (74.5% vs 60.6%, $p = 0.027$). Patients with larger stones (stone size 100 mm² or greater) had a greater benefit with treatment at 60 shocks per minute than those with smaller stones (71.1% vs 32%, $p = 0.002$, fig. 2). There was a trend toward a difference in stone-free rates between the 2 treatment groups. Stone-free rates were higher at 3 months in the 60 shocks per minute arm (56.4% vs 44.4%, $p = 0.064$). As with the treatment success rate, a more dramatic difference in the stone-free rate was seen for stones larger than 100 mm² in favor of the 60 shocks per minute arm (59.5% vs 28.0%, $p = 0.015$). Binary logistic regression modeling demonstrated that neither BMI, ureteral stent status, initial

TABLE 3. SWL outcomes

	No. SWL (%)		p Value
	60 Shocks/Min	120 Shocks/Min	
2-Wk posttreatment results:			
Overall success rate	87 (79.1)	73 (67.0)	0.043
Success for stones less than 100 mm ²	59 (80.8)	63 (75.0)	Not significant
Success for stones 100 mm ² or greater	28 (75.7)	10 (40.0)	0.005
Overall stone-free rate	36 (32.4)	32 (29.4)	Not significant
Stone-free rate for stones less than 100 mm ²	23 (31.5)	28 (33.3)	Not significant
Stone-free rate for stones 100 mm ² or greater	13 (34.2)	4 (16.0)	Not significant
3-Mo posttreatment results:			
Overall success rate*	82 (74.5)	66 (60.6)	0.027
Success for stones less than 100 mm ²	55 (76.4)	58 (69.0)	Not significant
Success for stones 100 mm ² or greater	27 (71.1)	8 (32.0)	0.002
Overall stone-free rate	66 (60.0)	48 (44.4)	0.064
Stone-free rate for stones less than 100 mm ²	44 (60.3)	41 (49.4)	Not significant
Stone-free rate for stones 100 mm ² or greater	22 (59.5)	7 (28.0)	0.015
SWL re-treatment for same stone within 3 mos	17 (17.7)	33 (32.4)	0.018
Ancillary procedure for same stone within 3 mos:			
Ureterscopy	3 (3.0)	3 (2.9)	Not significant
PCNL	1 (1.0)	0	Not significant

* Predefined primary outcome.

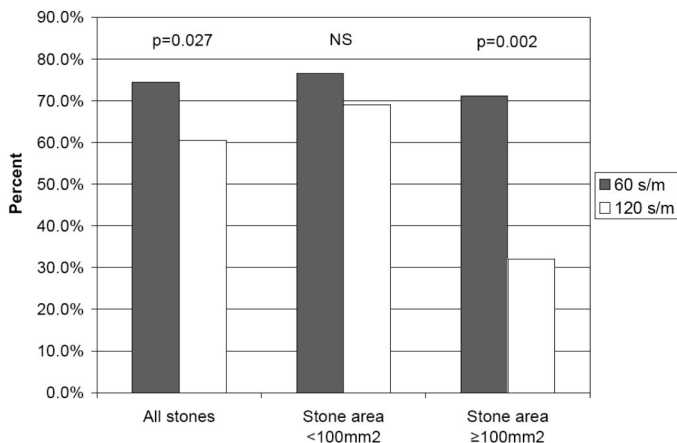


FIG. 2. SWL success rate at 3 months. NS, not significant. *s/m*, shocks per minute.

stone location nor treating urologist significantly affected SWL treatment success rate. Stone area was assessed before treatment, and again 2 weeks and 3 months after treatment. Stone area decreased more rapidly in patients treated with 60 shocks per minute compared with those who received 120 shocks per minute after adjusting for BMI and baseline stone size as covariates (repeated measures ANCOVA $F = 8.152$, $p = 0.005$).

Of patients treated with 120 shocks per minute 32.4% required a repeat SWL treatment within 3 months compared with only 17.7% of those treated with 60 shocks per minute ($p = 0.018$). There was no difference in the need for ancillary endourological procedures, such as ureteroscopy or PCNL, within 3 months of SWL between the 2 groups. There was a trend toward more complications in patients treated with 120 shocks per minute with an overall complication rate of 19.3% vs 10.8% ($p = 0.079$, table 4). The bulk of this difference was due to more visits to the emergency department for renal colic in patients treated with 120 shocks per minute (17 vs 10 patients, $p = 0.099$).

DISCUSSION

To our knowledge this randomized trial is the first to examine the impact of decreasing shock wave frequency on SWL outcome in humans. It demonstrates that SWL treatment at 60 shocks per minute provided more efficient stone fragmentation than treatment at the standard rate of 120 shocks per minute. This difference was more pronounced in patients with larger stones, namely those who currently have less favorable SWL outcomes with current treatment rates. In fact, patients with larger stones treated with 60 shocks per minute had success rates similar to those in patients with smaller stones. In addition, patients treated with 60 shocks per minute required fewer shocks to achieve stone fragmentation and were less likely to require additional SWL treatments to completely fragment the stone. SWL treatment at

60 shocks per minute did not lead to any increase in adverse events. Indeed, there was a trend toward fewer emergency room visits for renal colic in the 60 shocks per minute group, providing further evidence that patients in this group achieved greater stone fragmentation than patients treated with 120 shocks per minute.

For any given lithotripter the factors that can be controlled during SWL are the treatment rate, maximum voltage, voltage escalation rate, total number of shocks administered and stone targeting. The impact of rate on SWL efficacy has not been the subject of detailed study despite *in vitro* data suggesting a benefit dating back to 1989.⁹ The first generation of spark gap lithotriptors were synchronized with the patient ECG with a resulting shock wave rate of between 60 and 80 shocks per minute. With the next generation of spark gap lithotriptors ECG simulators were used to increase the shock wave rate to 120 shocks per minute and, thus, shorten treatment times. This was found to be safe¹⁰ but treatment outcomes were found to be inferior to those of first generation lithotriptors. This was generally considered to be due to the change in lithotripter technology but it may in fact have partly been due to the increase in the shock wave rate.

There are biological data to support the assertion that slower shock wave rates may improve stone comminution^{4,11} while decreasing renal damage.⁶ The mechanism for the increased efficiency of SWL at 60 shocks per minute remains unclear but it may be related to decreased acoustic impedance mismatch, improved cavitation bubble production on the stone surface or improved bubble dynamics due to water gas content surrounding the stone.⁵ The most likely explanation is related to the impact of the shock wave rate on cavitation bubbles. While spalling or the application of a tensile force within the stone upon shock wave reflection is an important mechanism of stone fragmentation,¹² there is increasing evidence to support that cavitation bubbles on the surface of the stone induced by SWL implode against the stone surface, developing high speed jets that erode the stone surface.¹³ In addition, high speed video photography has demonstrated bubbles forming and collapsing in cracks on the stone surface, suggesting that bubble expansion may act to enlarge these cracks.¹⁴ The inhibition of cavitation bubble formation with a viscous liquid,¹⁵ static pressure¹³ or a thin membrane placed on the stone surface¹⁶ dramatically inhibits stone fragmentation. Indeed, research lithotriptors specifically designed to increase cavitation lead to more damage to aluminum foil¹⁷ and stones¹⁸ *in vitro* and those designed to minimize cavitation decrease damage.¹⁷ Although cavitation bubbles in contact with the stone surface contribute to stone fragmentation, more remote cavitation bubbles may act as a barrier to efficient shock wave energy transmission. Slowing the shock wave rate may allow this barrier of bubbles to dissipate, allow increased gas content of the fluid medium adjacent to the stone and support better cluster bubble dynamics on the stone surface to promote superior fragmentation.

Since patients treated with 60 shocks per minute require fewer shocks and fewer SWL treatments to achieve stone fragmentation, complications related to renal parenchymal damage, such as hematoma and new onset hypertension, may occur less frequently in this group. It is clear that the number of shock waves administered, the maximum voltage applied and possibly the rate of voltage escalation during treatment contribute to renal injury. Decreasing shock wave frequency may minimize renal damage by requiring fewer total shocks and decreased re-treatment rates but it may have a more direct and beneficial effect on renal tissue by altering cavitation bubble dynamics. Allowing more time for bubble dissolution between shocks may minimize renal damage by avoiding capillary rupture.¹⁹

We chose the success rate rather than the stone-free rate as our primary outcome because the purpose of SWL is to

TABLE 4. SWL complications within 3 months of treatment

Complication	No. SWL (%)		p Value
	60 Shocks/ Min	120 Shocks/ Min	
Emergency room visit	10 (9.0)	17 (15.6)	0.099
Hospital admission	1 (0.9)	0	Not significant
Stent or nephrostomy insertion	1 (0.9)	1 (0.9)	Not significant
Steinstrasse	0	2 (1.8)	Not significant
Urinary tract infection	0	1 (0.9)	Not significant
Totals	12 (10.8)	21 (19.2)	0.079

fragment stones into sand or small fragments, which patients can pass spontaneously with minimal discomfort. This gives a better estimate of fragmentation efficiency and relies less on anatomical variations within the kidney that may prevent fragment clearance. Even when the stone-free rate was examined, there was a trend favoring 60 shocks per minute for all stones and a clear advantage in the stone-free rate for stones larger than 100 mm² treated with 60 shocks per minute. Of stones treated in this trial 50% were located in the lower calix, which explains in part the lower stone-free rate at 3 months because many patients had retained asymptomatic sand and small fragments following adequate fragmentation. This also explains why stone-free rates increased from the 2-week to the 3-month followup visit since in some patients small fragments were cleared from the calices. There was a slight but nonsignificant decrease in success rates from the 2-week to the 3-month followup visit. This occurred because the imaging modality at 3 months (renal tomography, noncontrast spiral CT or IVP with tomography) was more sensitive for retained fragments than the imaging modality at 2 weeks (plain x-ray of the kidneys, ureters and bladder only). As a result, 4.4% of patients in the 60 shocks per minute arm and 6.0% in the 120 shocks per minute arm were found to have had inadequate fragmentation (ie fragments 5 mm or larger). Interestingly the treatment of larger stones at 60 shocks per minute gave results comparable to those of smaller stones, so that the sharp decrease in the SWL success and stone-free rates for stones greater than 1 cm seen with treatment at 120 shocks per minute disappeared.

A consideration when interpreting the results of a randomized trial is determining the generalizability of the results. SWL treatment in Canada is highly regionalized and centralized. There are only 3 lithotriptors for a population of 12 million in the province of Ontario and our lithotripsy unit is the only unit for a catchment area of approximately 6 million people. As a result, our unit is one of the busiest in the world in terms of the number of treatments provided annually (approximately 2,600). This suggests that with such a broad referral base selection bias should be minimal and the results should be generalizable to other settings. A useful benchmark is to compare the results of treatment in the control arm (treatment at 120 shocks per minute) with broadly accepted results. The success and stone-free rates in the control arm (120 shocks per minute) of this trial compare favorably to those in studies showing the results of stone treatment with similar SWL generators and a similar stone distribution, ie a predominance of lower caliceal stones.²⁰

While treatment at 60 shocks per minute was more effective, there are practical considerations to decreasing the SWL rate. Mean treatment time was 16.4 minutes longer in patients in the 60 shocks per minute group. Since the bulk of the benefit of the slower treatment rate was seen in patients with a larger stone burden, it might be appropriate to use 60 shocks per minute in patients with larger stones, who achieve the most benefit.

CONCLUSIONS

During SWL for renal calculi decreasing the shock wave frequency from 120 to 60 shocks per minute results in improved fragmentation, particularly for larger stones. This decreases the need for additional SWL or more invasive treatment modalities without any increase in morbidity and with an acceptable increase in treatment time. Traditionally it was thought that there were relatively few aspects of SWL that could be varied by the treating urologist to maximize stone fragmentation. This trial demonstrates that decreasing the shock wave rate can improve stone fragmentation and potentially minimize renal injury, suggesting the exciting

possibility that modifying other parameters of SWL treatment may also improve outcomes.

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