The Effect of Shock Wave Rate on the Outcome of Shock Wave Lithotripsy: A Meta-Analysis

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Purpose: Although experimental evidence suggests that the rate of shock wave delivery can affect the outcome of shock wave lithotripsy, clinical studies produce conflicting results. We performed a systematic review and meta-analysis to define the effect of shock wave rate on the outcome of shock wave lithotripsy.

Materials and Methods: A search of MEDLINE and EMBASE was performed and all randomized controlled trials comparing SWL treatment at 60 shocks per minute to 120 shocks per minute were included in the analysis. Data from 4 trials (589 patients) were pooled. The primary outcome measure was treatment outcome (success, failure), as defined by the authors of the source studies. The difference in the proportion of patients with a successful treatment outcome was compared between the 60 and 120 shocks per minute groups as a risk difference, and risk differences were pooled across the 4 trials with a fixed effects model.

Results: Patients treated at a rate of 60 shocks per minute had a significantly greater likelihood of a successful treatment (risk difference 10.2, 95% CI 3.7–16.8, $p = 0.002$).

Conclusions: Our meta-analysis suggests that patients treated at a rate of 60 shocks per minute have a significantly greater likelihood of a successful treatment outcome than patients treated at a rate of 120 shocks per minute.

Key Words: kidney, calculi, lithotripsy, treatment outcome

The introduction of shock wave lithotripsy radically changed the treatment paradigm for upper urinary tract calculi. Stones that once required an open surgical procedure to effect cure could be treated by SWL in a completely noninvasive manner. Indeed, it is now estimated that approximately 70% of all symptomatic upper urinary tract calculi are treated with SWL.[1] Although initial reports of SWL found stone clearance rates to be quite good, recent investigations on the outcome of SWL have found that approximately half of patients treated with this modality do not clear their stone burdens.[2]

To improve the success rate of SWL, efforts have been devoted to defining what parameters the urologist can control, such as patient selection and treatment protocols, and what manipulations might improve the efficacy of the technology.[3] One of the parameters that has been the subject of a number of studies is the rate at which shock waves are delivered during SWL.[4–11] We performed a meta-analysis to define the effect that the rate of shock wave delivery has on the outcome of SWL.

MATERIALS AND METHODS

Study Search

Systematic searches of the MEDLINE and EMBASE databases (January 1966 to April 2007) were conducted using the terms lithotripsy and rate. The searches were limited to English language literature, and were performed by 2 investigators (MJS and BRM) independently of one another. Disagreements among the investigators were resolved by discussion.

Criteria for Inclusion

Criteria for inclusion were established a priori. Satisfying the criteria necessitated that the study objective was to investigate the effect of the rate of shock wave delivery, patients were randomized to a rate of 60 shocks per minute (1 Hertz) or 120 shocks per minute (2 Hertz) and the study recorded the treatment outcome. It was not necessary for the true stone-free rate to be recorded in the source study, and treatment success (yes vs no) as defined by each source study author was used as the primary outcome variable.

Data Extraction

Two reviewers (MJS and BRM) independently extracted data from each selected study with a standardized form. As in the study search, disagreements among the investigators were resolved by discussion. The specific definition of a successful outcome was recorded from each of the source studies, as it was expected that the definition of such an outcome measure would vary among studies.

Statistical Analysis

For each study the risk difference was defined as the absolute difference in treatment success rates between the 60 and 120 shocks per minute groups. The risk differences were pooled using a Mantel-Haenszel approach.[12] Risk differences were plotted for each study, with plotting symbols proportional to the Mantel-Haenszel weights. Heterogeneity among studies was evaluated using the I^2 statistic, which

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Randomized, controlled trials of the effect of shock wave rate on outcome of shock wave lithotripsy

References + Cohorts	No. Pts	Mean Pt Age	Stone Size	% Success	% Stone-Free
Pace et al:[8]					
Slow	111	49.2	84.4 mm^2	74.5*	56.4
Fast	109	50.7	80.4 mm^2	60.6*	44.4
Madbouly et al:[9]					
Slow	76	42	13.2 mm	98.7†	Not recorded
Fast	80	42.2	13.2 mm	90.0†	Not recorded
Yilmaz et al:[10]					
Slow	57	44	13.12 mm	89.5‡	Not recorded
Fast	56	40.5	14.02 mm	73.2‡	Not recorded
Davenport et al:[11]					
Slow	49	53	67 mm^2	59§	49
Fast	51	50	56 mm^2	61§	49

* Stone size less than 5 mm.
† Stone size less than 2 mm.
‡ Stone size less than 3 mm.
§ Stone size less than 4 mm.

estimates the percentage of variation across studies that is due to heterogeneity rather than chance. Values of I^2 less than 25% may be considered to represent a small degree of heterogeneity.[13] If the degree of heterogeneity was large (more than 50%) a random effects approach was used for pooling the risk differences.[14] Publication bias was assessed visually using a funnel plot, but due to the small number of studies this provides a highly subjective assessment. Therefore, the Egger bias statistic was calculated as well.[15] All calculations were performed using StatsDirect software, version 2.6.2 (StatsDirect Limited, Cheshire, United Kingdom).

RESULTS

Four studies were ultimately identified for inclusion in the review (see table).[8–11] The 4 trials were performed in 4 different countries. All 4 studies were randomized, although only 1 study described the method of randomization (random number generator tables).[11] Only 2 studies reported sample size calculations.[8,11] The inclusion criteria varied among the studies. Although all studies included only single radiopaque stones, the size criteria varied from greater than 5 mm,[8] to less than 20 mm,[10] to less than 30 mm,[9] to uncomplicated solitary renal calculi.[11] Mean treated stone size was reported as longest axis in 2 studies,[9,10] and stone surface area in the other 2 studies,[8,11] precluding comparisons of stone size among the 4 constituent studies. All studies except 1 included only renal calculi. Madbouly et al included renal and ureteral stones.[9] Three studies reported on stone location, but only 1 study characterized the effect of stone location on outcome.[8,10,11]

Each study used a different lithotriptor, namely the Stone Litho3pter (PCK, Turkey),[10] LithoTron (HealthTronics),[8] Siemens Lithostar Multiline (Siemens AG, Germany)[9] and Dornier Lithotripter S (Dornier MedTech, Germany).[11] The Litho3pter and the LithoTron are electrohydraulic devices, and the Siemens Lithostar and the Dornier Lithotripter S are electromagnetic devices. SWL treatment was performed with the patient under sedation,[11] with diclofenac analgesia with or without alfentanil,[8] with sedation plus local anesthesia[10] and with either general anesthesia or spinal/epidural anesthesia.[9] Treatment outcome was determined in 3 studies at the 3-month postoperative point[8,9,11] and in 1 study at the 10-day point.[10] To evaluate outcome 2 studies performed plain film and ultrasound,[10,11] 1 study performed plain x-ray, renal tomography, computerized tomography or excretory urography,[8] and 1 study performed plain x-ray only.[9]

Only 2 studies reported a true stone-free rate, with no fragments visible on plain abdominal x-ray.[8,11] However, all studies reported a success rate which was defined in several different ways as fragments less than 2 mm,[9] less than 3 mm,[10] less than 4 mm[11] and less than 5 mm.[8] Three studies observed a higher success rate with the 60 shocks per minute rate,[8–10] whereas 1 study observed similar success rates in both groups.[11] Only 1 study reported stone composition.[10]

Initial statistical review was performed with a fixed effects model, which demonstrated that patients who were treated at a rate of 60 shocks per minute experienced a 10.2% (95% CI. 3.7, 16.8) increase in the likelihood for a successful treatment outcome. This finding was statistically significant, $p = 0.002$ (fig. 1). There was no substantial heterogeneity among the studies, evidenced by Cochran's $Q = 2.41$ (3 df), $p < 0.490$, and $I^2 = 0\%$. Publication bias was evaluated graphically with a funnel plot and analyzed with Egger's test (fig. 2). There was no evidence of publication bias indicated by a lack of asymmetry in the funnel plot, and Egger's statistic $= -0.19$ ($p = 0.917$, fig. 2).

DISCUSSION

The initial work addressing the effect of shock wave rate on stone fragmentation was performed by Vallancien et al, who

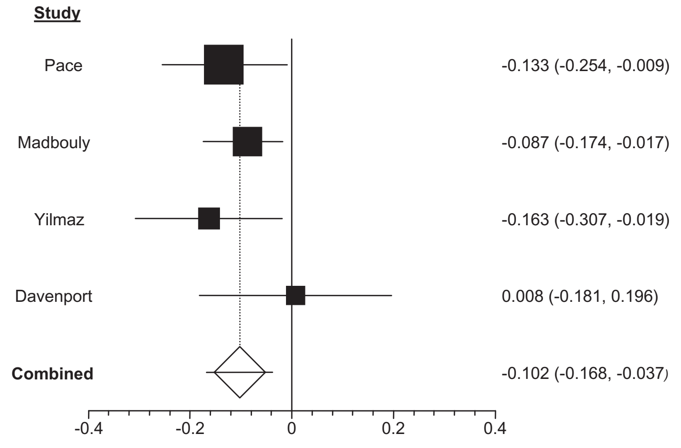

FIG. 1. Risk difference in proportion of successful lithotripsy procedures using fast vs slow rate (fixed effects model).

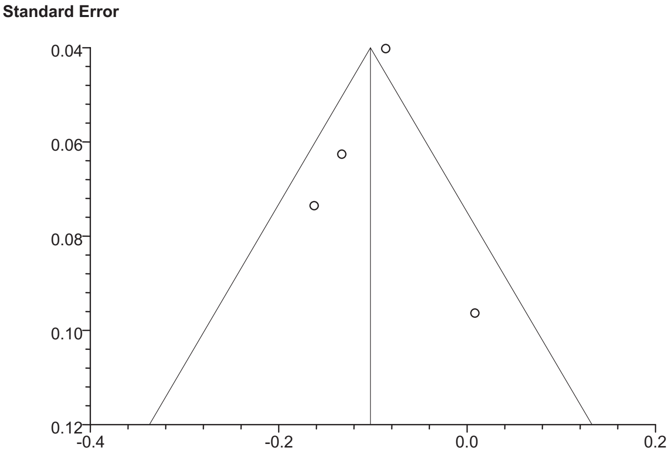

FIG. 2. Funnel plot to assess publication bias

used an in vitro piezoelectric model.[4] They reported that when kidney stones were subjected to varying rates of shock wave administration, stones treated at a slower frequency fragmented better than did stones treated at a faster frequency. These findings were replicated with in vitro electrohydraulic SWL models, which confirmed that 60 shocks per minute was the optimal frequency of shock wave administration.[5,6] The effect of shock wave rate was also examined with an in vivo porcine model.[7] This study used a reverse percutaneous nephrolithotomy study design, in which artificial gypsum stones were inserted via upper pole percutaneous access into the lower pole calix of the porcine kidney. The inserted stones were then treated with a Dornier HM3 device at either 30 or 120 shock waves per minute. In this model stones treated at a slower shock wave rate fragmented more completely, validating the findings of previous investigators.

The exact mechanism by which a slower shock wave rate may enhance stone comminution is not well understood. Cavitation, the formation and subsequent dynamic behavior of bubbles, may be induced by a lithotriptor generated pressure field.[16] The bubbles that are initiated by 1 shock wave do not typically persist through the arrival of the next shock wave.[17] However, inhomogeneities in the fluid that surrounds a stone, such as small fragments fractured off of the stone surface, will persist between shock waves and serve as nuclei, or promoters, of cavitation. As subsequent shock waves are delivered, the growth of cavitation bubbles seeded by these nuclei may draw energy from the negative pressure phase of the shock wave.[17] The ultimate consequence of such an effect may be reduced stone breakage.

Interestingly the initial clinical evaluation of a slow vs fast shock wave treatment rate was in the form of randomized controlled trials, which are included in the present meta-analysis. There are also several nonrandomized clinical series that have investigated the effect of slow vs fast treatment rate on SWL outcome. Kato et al treated 2 cohorts of patients, 1 at a rate of 60 shocks per minute and the other at a rate of 120 shocks per minute, in a nonrandomized fashion.[18] They found that the cohort of patients treated at the slower rate more often experienced effective stone fragmentation, although at 3-month followup there was no difference in treatment success. Chacko et al compared a group of patients treated at a rate of 70 to 80 shocks per minute to a group treated at 120 shocks per minute.[19] For stones 1 to 2 cm in size there was a significantly better outcome at the slower treatment rate, but for stones less than 1 cm the difference in outcome was not significant. Weiland et al analyzed more than 40,000 SWL procedures and compared the outcomes for patients treated with a slow rate, on average 79.6 shocks per minute vs a fast rate of 120 shocks per minute.[20] The patients treated at slower rate had a higher overall stone-free rate, and the calculated Efficiency Quotient was significantly greater for the slow rate group as well.

Several limitations of the source studies and, by extension, the present meta-analysis merit delineation. The number of studies is small, which limits the ability to evaluate the influence of factors that differ within patient subgroups or across studies. For example, the 4 source studies each used a different lithotriptor, and treatment outcomes may vary from lithotriptor to lithotriptor. Lithotripsy protocols, such as the various methods of anesthesia, also differed across the 4 studies. Stone size could not be compared across all 4 studies, due to the 2 methods of stone size measurement used. However, it is of interest that among all studies larger stones appeared to be affected by shock wave rate to a greater extent than smaller stones. Followup also was not constant for all 4 studies. Additionally, the definition of a successful treatment outcome varied among the studies, and the radiographic method of evaluation was not consistent. Nonetheless, analysis of these pooled studies demonstrates no significant heterogeneity, suggesting that a major consistent source of bias is unlikely. Furthermore, a meta-analysis of level I evidence (randomized controlled trial) is likely to minimize bias, as the evidence is evaluated in aggregate, as well as reduce the likelihood of random error, as the sample size is greater than that of any of the constituent trials.

CONCLUSIONS

SWL performed with a treatment rate of 60 shocks per minute is associated with a significantly higher rate of treatment success than SWL performed at a rate of 120 shocks per minute. Although different lithotriptors and treatment protocols were used in the randomized trials of the present meta-analysis, the effect of treatment rate on outcome is nonetheless significant. Further study should now be devoted to defining the effect of a slower treatment rate on the tissue injury caused by SWL in humans, as well as to determining other parameters that may be altered to improve treatment outcome.

Abbreviations and Acronyms

SWL = shock wave lithotripsy

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EDITORIAL COMMENT

The main problem with this meta-analysis is the comparison of 4 studies using 4 different machines, inclusion criteria and definitions of success. According to this meta-analysis a slower shock wave delivery rate of 60 shocks per minute improves outcome following lithotripsy for renal stones. Recent research suggests a slower rate may also reduce renal injury during lithotripsy.[1] It is worthwhile highlighting that stone size appears to affect outcome. By looking closer at the Pace et al data, the beneficial effect appears to be limited to those stones with an area greater than 100 mm^2 (reference 8 in article). Differences in success rates for stones smaller than this were nonsignificant, similar to the findings of our study (reference 11 in article). It also has to be remembered that a slower shock rate will increase treatment duration and may affect patient tolerance. A slower rate may be recommended for larger stones. However, the evidence for smaller stones is lacking at present.

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REPLY BY AUTHORS

We agree that the methodologies among the source studies are disparate, which can be important with a small meta-analysis of only 4 studies. The question is whether the methodologies differ to such an extent that they are not measuring the same phenomenon. We think the differences are not so profound. One of the strengths of a meta-analysis is that it allows data from diverse clinical trials to be synthesized to provide a broader perspective than is possible with data from a single institution or, in the present case, a single lithotriptor. Even with only 4 studies available, pooling the data enhances the power to detect relatively small, albeit clinically relevant effects, and limits the impact of individual biases.

Stone size is also important. Only Pace et al reported separate results for stones 100 mm^2 or greater and less than 100 mm^2, and only the former demonstrated a statistically significant improvement for the slower lithotripsy rate (reference 8 in article). We repeated the meta-analysis using their data for stones less than 100 mm^2, and noted a statistically significant improvement in the proportion of successes using the slower rate (pooled risk difference 7.8%, 95% CI 1.1, 14.4). We also analyzed whether stone size and the magnitude of the risk difference were correlated using maximum stone length as the size variable, and found no significant association across the studies. In the study by Davenport et al (reference 11 in article), who used size as the product of length $\times$ width, we assumed length = width, as this would give the most conservative result, ie the smallest value for maximum length.

It may be that the effect of a slower rate is less pronounced for patients with smaller stones, and it will be important for future authors to analyze results for small and large stone subgroups with adequate power. However, it is worth considering the entirety of the raw data of our analysis, because there have been no reports of an inferior outcome associated with a slower treatment rate (even within the subset with smaller stones in the study by Pace et al). Furthermore, the pooled data do suggest a clinically and statistically significant benefit for a slower treatment rate. However, the improvement in treatment outcome does have a price, which is increased treatment time.