Optimization of Treatment Strategy Used During Shockwave Lithotripsy to Maximize Stone Fragmentation Efficiency

Daniel Z. Yong, B.S.,¹ Michael E. Lipkin, M.D.,¹ W. Neal Simmons, Ph.D.,² Georgy Sankin, Ph.D.,²
David M. Albala, M.D.,¹ Pei Zhong, Ph.D.,² and Glenn M. Preminger, M.D.¹

Abstract

Background and Purpose: Previous studies have demonstrated that treatment strategy plays a critical role in ensuring maximum stone fragmentation during shockwave lithotripsy (SWL). We aimed to develop an optimal treatment strategy in SWL to produce maximum stone fragmentation.

Materials and Methods: Four treatment strategies were evaluated using an *in-vitro* experimental setup that mimics stone fragmentation in the renal pelvis. Spherical stone phantoms were exposed to 2100 shocks using the Siemens Modularis (electromagnetic) lithotripter. The treatment strategies included increasing output voltage with 100 shocks at 12.3 kV, 400 shocks at 14.8 kV, and 1600 shocks at 15.8 kV, and decreasing output voltage with 1600 shocks at 15.8 kV, 400 shocks at 14.8 kV, and 100 shocks at 12.3 kV. Both increasing and decreasing voltages models were run at a pulse repetition frequency (PRF) of 1 and 2 Hz. Fragmentation efficiency was determined using a sequential sieving method to isolate fragments less than 2 mm. A fiberoptic probe hydrophone was used to characterize the pressure waveforms at different output voltage and frequency settings. In addition, a high-speed camera was used to assess cavitation activity in the lithotripter field that was produced by different treatment strategies.

Results: The increasing output voltage strategy at 1 Hz PRF produced the best stone fragmentation efficiency. This result was significantly better than the decreasing voltage strategy at 1 Hz PFR (85.8% vs 80.8%, $P=0.017$) and over the same strategy at 2 Hz PRF (85.8% vs 79.59%, $P=0.0078$).

Conclusions: A pretreatment dose of 100 low-voltage output shockwaves (SWs) at 60 SWs/min before increasing to a higher voltage output produces the best overall stone fragmentation *in vitro*. These findings could lead to increased fragmentation efficiency *in vivo* and higher success rates clinically.

Introduction

SHOCKWAVE LITHOTRIPSY (SWL) has been the first-line treatment for renal and ureteral stones during the last two decades. SWL is a minimally invasive procedure with low morbidity and good efficacy. The primary goal of SWL is to disintegrate stones to small fragments for spontaneous passage with minimal injury to surrounding tissues. An optimal treatment protocol to maximize stone fragmentation while minimizing tissue injury has yet to be established. Several previous studies have demonstrated that treatment strategy plays a critical role in ensuring maximum stone comminution with minimal tissue injury in SWL.^{1,2}

In this study, we determined the characteristics of shockwaves (SWs) at different voltage outputs and pulse repetition frequencies (PRFs) using a fiberoptic hydrophone and high-speed camera. We investigated four treatment strategies for SWL with an *in-vitro* model mimicking a stone in the renal pelvis.

Material and Methods

Cavitation assessment and pressure waveform measurement

Cavitation activity produced in the lithotripter field was measured by high-speed imaging using a phantom camera (Phantom v.7.3, Vision Research, Wayne, NJ) at a frame rate of up to 50,000 frames/s and an exposure time of 19 μ s. A schematic diagram of the experimental setup is shown in Figure 1, and details can be found in previously published studies.^{3,4} Two digital delay generators (DG 535, Stanford Research Systems) were used to trigger the electromagnetic SW source (Modularis, Siemens USA, Malvern, PA) and high-speed camera, respectively. A fiberoptic hydrophone (FOPH-500, RP acoustics, Leutenbach, Germany) was also connected to a 100 MHz digital oscilloscope (TDS 2014, Tektronix, Beaverton, OR). The 100 μ m probe tip of the FOPH-500 was placed at 10 mm from the SW focus to measure the pressure waveforms that were recorded by the oscilloscope at a

¹Department of Surgery, Division of Urology, Duke University Medical Center, Durham, North Carolina.

²Therapeutic Research Laboratory, Pratt School of Engineering, Duke University, Durham, North Carolina.

FIG. 1. Diagram of cavitation assessment and pressure waveform measurement experimental setup. (1) Modularis shock head; (2) Water tank with 20 L degassed water; (3) optic fiber of the FOPH 500 with tip at focus; (4) phantom camera.

sampling rate of 100 MHz. Temperature of the SW source was kept within 4°C of room temperature by a water-cooling system.

Two different treatment strategies were evaluated using a total of 2,100 SWs at 1 Hz. In the first group, an increasing output voltage was used with 100 shocks at 12.3 kV (low setting), 400 shocks at 14.8 kV (high setting), and 1600 shocks at 15.8 kV (high setting). In the second group, a decreasing output voltage was performed with 1600 shocks at 15.8 kV, 400 shocks at 14.8 kV, and 100 shocks at 12.3 kV. A sample size of five was used for each group.

Cavitation activity was quantified using Matlab to process the acquired images at 250 μ s post-trigger of shock, the time of maximum prefocal cavitation activity as determined through preliminary investigations. Cavitation activity was measured as the fraction of an area of interest filled with bubbles.

Stone fragmentation test

Spherical stone phantoms (10 mm) with acoustic and mechanical properties similar to calcium oxalate monohydrate stones were made from BegoStone (Bego USA, Smithfield, RI) using a powder-to-water ratio of 5:1.⁵ Each stone phantom was weighed in a dry state and then immersed in degassed water (O_2 concentration < 3 mg/L) for at least 4 hours before testing.

The stone fragmentation test was performed using a phantom system that mimics stone comminution in the renal pelvis.^{1,6,7} Stone phantoms were placed in a 30-mm membrane holder consisting of a cylindrical plastic holder with a silicone rubber membrane flat bottom. Such a holder mimics clinical stone movement allowing for some lateral dispersal of stone fragments. A digital camera (Homeconnect 0770, 3Com, Marlborough, MA) was also mounted directly above the stone holder to monitor dynamic process of stone fragmentation during SWL.⁸

Four treatment strategies were evaluated using the Siemens Modularis lithotripter. The treatment strategies included increasing output voltage with 100 shocks at 12.3 kV, 400

shocks at 14.8 kV, and 1600 shocks at 15.8 kV, and decreasing output voltage with 1600 shocks at 15.8 kV, 400 shocks at 14.8 kV, and 100 shocks at 12.3 kV. Both increasing and decreasing voltages models were run at 1 and 2 Hz with a sample size of 12 in each configuration. The lithotripter output voltage of 12.3 kV, 14.8 kV, and 15.8 kV are usual clinical energies used in the treatment of renal stones.⁹ After SW treatment, stone fragments were collected and dried in air for 24 hours. Fragmentation efficiency was determined using a sequential sieving method to isolate fragments less than 2 mm. The Student *t* test was performed to determine the statistical difference among the test groups.

Results

Initial cavitation assessment and pressure waveform measurements with 60 SWs

The phantom high-speed camera was used to capture cavitation activity along the path of the SWs, and the 250 μ s post-trigger frames are displayed in Figure 2. Using these frames, the cavitation activity within the prefocal area was calculated with Matlab. Cavitation activity increased when SWs were initiated and stabilized after approximately 10 shocks. To assess the prefocal cavitation activity during high voltage outputs (14.8 kV) of each treatment strategy, results from the 11th to 30th high-voltage output SWs were averaged. A “low- to high-voltage output” strategy showed significantly less prefocal cavitation activity than a “high- to low-voltage output” strategy at 1 Hz (0.783 vs 0.807, $P=0.0385$). At 2 Hz, there was no significant difference between both strategies.

Cavitation assessment with 2100 SWs at 1 Hz

The first 50 SWs at 15.8 kV had significantly lower prefocal cavitation activity in the low- to high-voltage output strategy when compared with the high- to low-voltage strategy (0.752 vs 0.8236, $P=0.0466$). The subsequent 50 SWs showed a trend toward lower prefocal cavitation activity in the low- to high-voltage output strategy (0.766 vs 0.827, $P=0.0666$). After 100 SWs, there was no significant difference in prefocal cavitation between the two strategies.

Stone fragmentation

The increasing output voltage strategy at 1 Hz (Escal 1Hz) had the best stone fragmentation efficiency (Figure 3). This strategy showed significantly improved fragmentation efficiency over the decreasing voltage model at 1 Hz (DeEscal 1 Hz) (85.8% vs 80.8%, $P=0.017$) and over the same strategy at 2 Hz (Escal 2 Hz) (85.8% vs 79.59%, $P=0.0078$). Overall, when comparing 1 Hz vs 2 Hz, stone fragmentation efficiency was significantly better for 1 Hz (83.6% vs 79.2%, $P=0.0175$).

Discussion

In SWL, the two fundamental mechanisms that are known to contribute to stone fragmentation are stress waves and cavitation. Stress waves can initiate fragmentation at low output voltages but play a smaller role when fragments are less than half the wavelength of the stone material (about 4.4 mm in BegoStone phantoms).^{1,10} Cavitation is induced by the tensile component of the SWs and causes surface erosion of the stone when the cavitation bubbles collapse to form

FIG. 2. Cavitation activity produced along the path of the shockwave: (A) 30 shocks at 12.3V followed by 30 shocks at 14.8V at 1 Hz; (B) 30 shocks at 14.8V followed by 30 shocks at 12.3V at 1 Hz; (C) and (D) at 2 Hz.

microjets.^{11,12} Treatment strategies differ in the use of stress wave and cavitation forces. An optimal treatment strategy is one that incorporates both mechanisms to work synergistically to maximize stone fragmentation.

Decreasing the rate of SW delivery has been shown to result in improved stone comminution *in vitro*^{13,14} and *in vivo*.¹⁵ Clinical studies, including a meta-analysis of four randomized controlled trials, have observed higher success rates when implementing a rate of 60 SWs/min compared with previous standards of 120 SWs/min.¹⁶ An increased delivery rate leads to a greater attenuation of the tensile component of the SW, thus leading to a reduction in the effectiveness of cavitation at the stone surface toward fragmentation.^{17,18}

A delayed stepwise SW voltage escalation has also shown improved stone comminution *in vitro* and *in vivo*.^{1,19} As disintegration of the stone occurs, fragments accumulate and cause scatter and attenuation of subsequent SWs.¹⁰ A priming

dose of low voltage SWs may not lead to immediate comminution but would cause microfractures on the surface of the stone. The weakened stone will then crumble readily into more uniformly distributed fragments once the voltage output of the lithotripter is increased, thus compensating for the effects of scatter and attenuation. A stronger SW in the latter part of treatment will also enhance cavitation activity, which plays a large role in comminution of smaller fragments.

In this study, cavitation assessment demonstrated that by starting with 30 low voltage SWs, the prefocal cavitation activity of subsequent high voltage SWs was reduced. Prefocal cavitation results from the maturation of cavitation nuclei,^{20–22} which stems from small particles suspended in fluid or residuals of bubbles from previous cavitation clusters.²³ Cavitation nuclei can be deactivated or consumed by acoustic SWs. Below a negative pressure (tensile component of the SW) threshold, the pool of cavitation nuclei depletes with each SW administered.^{24,25} Therefore, it is conceivable that a pretreatment dose of low voltage SWs deactivates the cavitation nuclei in the prefocal area, thus reducing the prefocal cavitation activity when high voltage SWs are administered. This phenomenon, however, was not seen at 2 Hz, suggesting that a low voltage and slow delivery rate is needed for prefocal cavitation nuclei deactivation.

Although cavitation is desired at the focus to enhance stone fragmentation, its activity in the prefocal area is detrimental to comminution. Abundant prefocal cavitation fields can cause a reduction of the negative-pressure phase (tensile component) of the SW,^{17,18} which was consistent with the observed pressure waveform measurements of this study. Although the difference in waveforms is not as pronounced as previous

FIG. 3. Stone fragmentation efficiency rates (% of stone fragments <2 mm) of four treatment strategies evaluated.

studies, this is probably because of measurements being taken away from the SW focus. To enable the gathering of measurements for 60 SWs at a high voltage output, the fiberoptic tip was placed 10 mm from focus and would be damaged if placed at focus. The growth of cavitation nuclei draws energy from the negative-pressure phase of SW, reducing its amplitude. Trailing negative pressure is needed for focal cavitation at the interface between stone and fluid.²⁶ Thus, a reduction in negative trailing pressure results in lower focal cavitation and therefore reduced stone breakage.

Indeed, stone fragmentation analysis showed that the optimal treatment strategy for stone comminution efficiency in a modern electromagnetic lithotripter is one that incorporated pretreatment at a low voltage output and slower delivery rate before increasing to a high voltage output for treatment. These results are consistent with previous *in-vitro* and *in-vivo* studies in the HM-3 lithotripter.^{1,19}

Existing clinical studies have reached differing conclusions on the efficacy of a delayed stepwise SW voltage escalation strategy.^{27–30} This may be because of the inherent large variations in the characteristics of the patients and in stone composition, size, and location. Another possible reason is the use of different lithotripters, which could lead to different voltage output settings. The low output voltage SWs performed may be insufficient to cause acoustic clearing of cavitation nuclei or microfractures for priming, resulting in a negative study.²⁹ In addition, prolonged low voltage settings or the incorporation of intermediate output voltages could negate the advantageous effects of using a low priming dose.³⁰ In this study, a pretreatment dose of 100 low voltage SWs at 1 Hz was found to be sufficient to achieve superior stone comminution efficiency. These findings may provide a basis to the refinement of voltage escalation or stepwise strategies that have been previously tested.

In this *in-vitro* study, the prefocal area consisted of degassed water, which has a different cavitation potential compared with tissue. The advantageous effects of cavitation nuclei deactivation may not be as significant *in vivo*. Further confirmation with animal studies is needed. Nevertheless, prefocal cavitation remains a factor, because it may occur in the coupling cushion of the lithotripter or the vasculature of tissue.^{2,31}

Conclusions

A pretreatment dose of 100 low energy SWs at 60 SWs/min before increasing to a higher energy produces the best overall stone fragmentation *in vitro*. These findings could lead to an improved treatment strategy with concomitant increase in fragmentation efficiency *in vivo* and higher success rates clinically.

Disclosure Statement

No competing financial interests exist.

References

1. Zhou Y, Cocks FH, Preminger GM, Zhong P. The effect of treatment strategy on stone comminution efficiency in shock wave lithotripsy. *J Urol* 2004;172:349–354.
2. McAteer JA, Bailey MR, Williams JC Jr, et al. Strategies for improved shock wave lithotripsy. *Minerva Urol Nefrol* 2005;57:271–287.
3. Sankin GN, Simmons WN, Zhu SL, Zhong P. Shock wave interaction with laser-generated single bubbles. *Phys Rev Lett* 2005;95:034501.
4. Klaseboer E, Fong SW, Turangan CK, et al. Interaction of lithotripter shockwaves with single inertial cavitation bubbles. *J Fluid Mech* 2007;593:33–56.
5. Liu Y, Zhong P. BegoStone—a new stone phantom for shock wave lithotripsy research. *J Acoust Soc Am* 2002;112:1265–1268.
6. Zhong P, Zhou Y. Suppression of large intraluminal bubble expansion in shock wave lithotripsy without compromising stone comminution: Methodology and in vitro experiments. *J Acoust Soc Am* 2001;110:3283–3291.
7. Zhou Y, Zhong P. Suppression of large intraluminal bubble expansion in shock wave lithotripsy without compromising stone comminution: Refinement of reflector geometry. *J Acoust Soc Am* 2003;113:586–597.
8. Qin J, Simmons WN, Sankin G, Zhong P. Effect of lithotripter focal width on stone comminution in shock wave lithotripsy. *J Acoust Soc Am* 2010;127:2635–2645.
9. Egilmez T, Tekin MI, Gonen M, et al. Efficacy and safety of a new-generation shockwave lithotripsy machine in the treatment of single renal or ureteral stones: Experience with 2670 patients. *J Endourol* 2007;21:23–27.
10. Zhu S, Cocks FH, Preminger GM, Zhong P. The role of stress waves and cavitation in stone comminution in shock wave lithotripsy. *Ultrasound Med Biol* 2002;28:661–671.
11. Zhong P, Chuong CJ, Preminger GM. Propagation of shock waves in elastic solids caused by cavitation microjet impact. II: Application in extracorporeal shock wave lithotripsy. *J Acoust Soc Am* 1993;94:29–36.
12. Zhong P, Chuong CJ. Propagation of shock waves in elastic solids caused by cavitation microjet impact. I: Theoretical formulation. *J Acoust Soc Am* 1993;94:19–28.
13. Weir MJ, Tariq N, Honey RJ. Shockwave frequency affects fragmentation in a kidney stone model. *J Endourol* 2000;14:547–550.
14. Greenstein A, Matzkin H. Does the rate of extracorporeal shock wave delivery affect stone fragmentation? *Urology* 1999;54:430–432.
15. Paterson RF, Lifshitz DA, Lingeman JE, et al. Stone fragmentation during shock wave lithotripsy is improved by slowing the shock wave rate: Studies with a new animal model. *J Urol* 2002;168:2211–2215.
16. Semins MJ, Trock BJ, Matlaga BR. The effect of shock wave rate on the outcome of shock wave lithotripsy: A meta-analysis. *J Urol* 2008;179:194–197.
17. Pishchalnikov YA, McAteer JA, Williams JC Jr, et al. Why stones break better at slow shockwave rates than at fast rates: In vitro study with a research electrohydraulic lithotripter. *J Endourol* 2006;20:537–541.
18. Pishchalnikov YA, McAteer JA, Williams JC Jr. Effect of firing rate on the performance of shock wave lithotripters. *BJU Int* 2008;102:1681–1686.
19. Maloney ME, Marguet CG, Zhou Y, et al. Progressive increase of lithotripter output produces better in-vivo stone comminution. *J Endourol* 2006;20:603–606.
20. Harvey EN, Barnes DK, McElroy WD, et al. Bubble formation in animals I. Physical factors. *J Cell Compar Physl* Aug 1944;24(1):1–22.
21. Harvey EN, McElroy WD, Whiteley AH, et al. Bubble formation in animals III. An analysis of gas tension and hydrostatic pressure in cats. *J Cell Compar Physl* 1944;24:117–132.

22. Harvey EN, Whiteley AH, McElroy WD, et al. Bubble formation in animals II. Gas nuclei and their distribution in blood and tissues. *J Cell Compar Physl* 1944;24:23–34.
23. Arora M, Junge L, Ohl CD. Cavitation cluster dynamics in shock-wave lithotripsy: Part 1. Free field. *Ultrasound Med Biol* 2005;31:827–839.
24. Borkent BM, Arora M, Ohl CD. Reproducible cavitation activity in water-particle suspensions. *J Acoust Soc Am* 2007;121:1406–1412.
25. Borkent BM, Gekle S, Prosperetti A, Lohse D. Nucleation threshold and deactivation mechanisms of nanoscopic cavitation nuclei. *Phys Fluids* 2009;21:1020031–1020039.
26. Weizer AZ, Zhong P, Preminger GM. New concepts in shock wave lithotripsy. *Urol Clin North Am* 2007;34:375–382.
27. Demirci D, Sofikerim M, Yalcin E, et al. Comparison of conventional and step-wise shockwave lithotripsy in management of urinary calculi. *J Endourol* 2007;21:1407–1410.
28. Lambert EH, Walsh R, Moreno MW, Gupta M. Effect of escalating versus fixed voltage treatment on stone comminution and renal injury during extracorporeal shock wave lithotripsy: A prospective randomized trial. *J Urol* 2010;183:580–584.
29. You D, Park J, Hong B, Park HK. Effect of output voltage distribution on stone comminution efficiency during shock-wave lithotripsy in renal or ureteropelvic junction stones: A preliminary study. *Scand J Urol Nephrol* 2010;44:236–241.
30. Honey RJ, Ray AA, Ghiculete D, Pace KT. Shock wave lithotripsy: A randomized, double-blind trial to compare immediate versus delayed voltage escalation. *Urology* 2010;75:38–43.
31. Handa RK, Bailey MR, Paun M, et al. Pretreatment with low-energy shock waves induces renal vasoconstriction during standard shock wave lithotripsy (SWL): A treatment protocol known to reduce SWL-induced renal injury. *BJU Int* 2009;103:1270–1274.

Address correspondence to:
Michael E. Lipkin, M.D.
Duke University Medical Center
DUMC 3167
Durham, NC 27710

E-mail: michael.lipkin@duke.edu

Abbreviations Used

PRF = pulse repetition frequency
 SW = shockwave
 SWs = shockwaves