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

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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.

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 μs. A schematic diagram of the experimental setup is shown in Figure 1, and details can be found in previously published studies. 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 2024, Tektronix, Beaverton, OR). The 100 μm 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
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 μs post-trigger of shock, the time of maximum precavitation 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 7:1. Each stone phantom was weighed in a dry state and then immersed in degassed water (O2 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. 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.

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. 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 μs 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 1st to 30th high-voltage output SWs were averaged. A “low- to high-voltage output” strategy showed significantly less precavitation activity than a “high- to low-voltage output” strategy at 1 Hz (0.733 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 precavitation 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 precavitation 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 precavitation between the two strategies.

**Stone fragmentation**

The increasing output voltage strategy at 1 Hz (Escal 1 Hz) had the best stone fragmentation efficiency (Figure 3). This strategy showed significantly improved fragmentation efficiency over the decreasing voltage model at 1 Hz (Defscal 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 mm in BegoStone phantoms). Cavitation is induced by the tensile component of the SWs and causes surface erosion of the stone when the cavitation bubbles collapse to form...
microjets.\textsuperscript{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 \textit{in vitro}\textsuperscript{13,14} and \textit{in vivo}.\textsuperscript{15} Clinical studies, including a meta-analysis of four randomized controlled trials, have observed higher success rates when implementing a rate of 60\textit{SW}s/\textit{min} compared with previous standards of 120\textit{SW}s/\textit{min}.\textsuperscript{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.\textsuperscript{17,18}

A delayed stepwise SW voltage escalation has also shown improved stone comminution \textit{in vitro} and \textit{in vivo}.\textsuperscript{14} As disintegration of the stone occurs, fragments accumulate and cause scatter and attenuation of subsequent SWs.\textsuperscript{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,\textsuperscript{20-22} which stems from small particles suspended in fluid or residuals of bubbles from previous cavitation clusters.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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

![Stone fragmentation efficiency rates (% of stone fragments <2 mm) of four treatment strategies evaluated.](image-url)
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 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. Trailling negative pressure is needed for focal cavitation at the interface between stone and fluid. 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.

Existing clinical studies have reached differing conclusions on the efficacy of a delayed stepwise SW voltage escalation strategy. This may be because of the inherent large variatons 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. In addition, prolonged low voltage settings or the incorporation of intermediate output voltages could negate the advantageous effects of using a low priming dose. 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 prefocus 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, prefocus cavitation remains a factor, because it may occur in the coupling cushion of the lithotripter or the vasculature of tissue.

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


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Abbreviations Used
PRF = pulse repetition frequency
SW = shockwave
SWs = shockwaves