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The Impact of Fluid Environment Manipulation on Shockwave Lithotripsy Artificial Calculi Fragmentation Rates

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Abstract

Background and Purpose: Studies have suggested that shockwave lithotripsy (SWL) stone fragmentation rates can be affected by characteristics of the fluid media surrounding the stone, although evidence to implicate the impact of urine specific gravity (SG) is limited and inconclusive. Our aim is to further explore the impact fluid media and SGs have on stone fragmentation using a variable focus lithotripter.
Materials and Methods: Artificial stones were presoaked for 24 hours in urine and then shocked in various fluid media including artificial urine (SG 1.010 control, 1.020, and 1.07), human pooled urine (HPU), degassed HPU, Pentastarch, 100% and 30% contrast, degassed 30% contrast, 100% ethanol, deionized water (dH_2O), degassed dH_2O, 5% glucose, Ringer lactate, 0.9% saline, glycerol, whole blood, and lubricating gel. After soaking, SWL using the Modulith SLX-F2 electromagnetic lithotripter was performed. Fragments were dried and sieved using a 4-mm diameter opening grid. Fragments >4 mm were weighed and fragmentation coefficients (FCs) calculated (pre-SWL weight – post-SWL weight)/(pre-SWL weight)×100. Fifteen stones were shocked for each fluid group.
Results: Fluid type, viscosity, and degassing all significantly impacted stone fragmentation. While the solutions' SG, per se, did not appear to affect stone fragmentation, the use of degassed 30% contrast significantly improved stone destruction over the SG 1.010 artificial urine control (95.3% *vs* 71.4, $P < 0.01$). Furthermore, degassing improved comminution rates by increasing the number of completely fragmented stones (FC = 100%). Using degassed 30% contrast, 12/15 stones were completely fragmented, compared with only 2/15 in the control group ($P = 0.007$). Among the whole blood, glycerol, and lubricating gel groups, only 1/15, 0/15, and 1/15 stones reached 100% FC respectively in the narrow focus, possibly because of the detrimental impact of increased viscosity.
Conclusions: Different fluid media can significantly affect FC *in vitro*. Among the various fluids tested, degassed 30% contrast significantly increased the FC and total number of completely fragmented stones.

Introduction

Recent data suggest that approximately 70% of upper urinary tract calculi are managed by shockwave lithotripsy (SWL).[1] With further evolution of this technology, more powerful, compact, and anesthesia-free lithotripters have been developed. Despite the technologic advancements, however, a paradoxic phenomenon has been observed, in that newer machines cannot match the clinical outcomes of the original HM-3 lithotripter.

Multiple mechanisms for the comminution of urinary calculi submitted to SWL have been proposed, including cavitation effects (microjets and acoustic emissions from collapsing bubbles) and noncavitational mechanical forces, such as spallation, compression, and shear.[2] Experimental findings have shown that the manipulation of these physical principles can have an impact on stone fragmentation. Delius[3] and Pishchalnikov and associates[4] have both shown that experimental stone damage can be reduced by decreasing cavitation through overpressure[3] or shockwave (SW) timing.[4]

Interventions that involve the fluid surrounding the stone have received less attention, with a very limited list of fluid types[5,6] and inconclusive results.[7] We report our findings on the potential effect of various fluid types surrounding stones during SWL.

Materials and Methods

Cylindrical artificial urinary calculi were prepared using Begostone Plus plaster with a powder to water ratio of 5:1 (Bego Canada, Quebec City, QC, Canada), weighing 2 g (±0.1) and approximately 13 mm in diameter×8 mm thick.

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We randomly selected a sample of phantoms to undergo cross-sectional imaging (CT) to document Hounsfield units (HUs) and heterogeneity.

The stone phantoms were soaked in human pooled urine (HPU) for at least 24 hours. After this period, one stone was placed in each of the five testing wells of a tissue simulating scaffold made of 10% gelatin. After SWL, the fragments were collected from each test well and air dried for 24 hours in a 37°C incubator. Fragments were sifted using the middle section of a 20 to 200 uL pipette tip box (VWR) containing 4-mm diameter openings, and all fragments passing through were discarded. The remaining fragments were weighed, and the fragmentation coefficient (FC) of each stone was calculated using the following formula: (Pre-SWL weight–post-SWL weight)/(pre-SWL weight)×100.[8] Data were analysed using the Student *t* test (two groups; eg, HU analysis) and Kruskal-Wallis with the Dunn post-test (multiple groups; eg, FC rates) for nonparametric data, and chi square (multiple groups) test (eg, complete fragmentation rates) using GraphPad Prism4 software (GraphPad Software Inc., San Diego, CA).

Eighteen different media were tested in the study (Table 1). Fluids were selected for evaluation based on their relevance to clinical scenarios: Specific gravity (SG) and density (artificial urine [AU] SG 1.01, 1.02, 1.07, ethanol [EtOH], glycerol [Gly], deionized water [dH_2O], and lubricating jelly [LJ]), presence in the urinary tract during SWL (contrast, HPU, whole blood [WB]) or biocompatibility (saline, 5% glucose [Glu], Pentastarch, and Ringer lactate). AU was produced as per Brooks and Keevil.[9] Degassing was performed by subjecting the testing fluid to a decreased atmospheric pressure (~30 mm Hg) in a vacuum chamber for a minimum of 4 hours. All degassed fluids were used within 30 minutes.

Lithotripsy was conducted using the Modulith SLX-F2 "dual focus" lithotripter (Storz Medical AG, Tägerwilen, Switzerland). The standardized protocol consisted of 1000 SWs at an energy level of 8 and a frequency of 120 SW/min. The narrow (standard) treatment focus (NF) was used for half of the phantoms and the wide (large) focus (WF) for the remaining half. The F2 diameters were 6 mm×28 mm in the NF *vs* 9 mm×50 mm in the WF (technical data, Storz Medical AG). Stone targeting was performed using biplanar fluoroscopy.

Results

A total of 540 stones were shocked, 30 in each of the 18 experimental groups. Fourteen stones were randomly selected and underwent CT. No grossly apparent heterogenic areas were found that would suggest aberrant cement concentration or air pockets. HU measurements were made at three sites of each stone (proximal, mid, and distal) using an elliptic region of interest tool and 8x zoom, to encompass the whole stone diameter. The three measurements were then averaged, and the results divided into two groups (high and low HU, median at 1818 HU). The mean HU were 1852 and 1745 ($P = 0.78$) for the high and low groups, respectively.

The mean overall FC of the groups is depicted in Figure 1. The degassed contrast (DGC) group significantly increased the FC ($P < 0.05$), while Gly and LJ had the opposite effect ($P < 0.001$). When using the NF, the mean FC for the control group (group 1) was 62.4% (range 5–100). The FC was significantly increased when using DGC (mean 95.3%, $P < 0.01$). The FC was significantly decreased when using LJ (mean 14.2%) and Gly (mean 17.12%) (both $P < 0.05$). For the remaining groups, the mean FC was not significantly different (Table 2). When using the WF, the mean FC of the control group was 76.4%. The use of LJ (mean 13.6%, $P < 0.001$), Gly (mean 34.4%, $P < 0.01$), and Glu (mean 41.3%, $P < 0.05$) significantly decreased the FC. In the rest of the groups, the mean FC was not significantly different (Table 2).

Further analysis with chi square revealed that the number of stones with complete fragmentation (CF) (FC 100%) was also impacted by fluid type in both the NF and WF ($P < 0.0001$) (Table 3). In the NF, DGC achieved 12/15 CF, a significant enhancement over the control group (CF 2/15, $P = 0.0007$) and the rest of the experimental groups, aside from 30% C and $DGdH_2O$ (CF 6/15 each) where a trend toward statistical significance was seen ($P = 0.06$). With the WF, the control group's CF rate was 1/15 while $DGdH_2O$ CF was

Table 1. Test Fluids

Group	*Fluid characteristics*	*Specific gravity*
Control	Artificial urine	1.01
HPU	Human pooled urine	1.01–1.02
LJ	Water-based lubricating jelly (Healthcare plus, Toronto)	1.01
Penta	Pentastarch (Pentaspan, Bristol-Myers Squibb Canada, Montreal)	1.01
30% C	30% Contrast (4.5 ml of Conray 43 and 10.5 ml of 0.09% normal saline)	1.07
AU1.02	Artificial urine pH 6.5	1.02
EtOH	100% ethanol	.789
100% C	100% contrast (Conray 43, Tyco Healthcare, Canada)	1.22
Gly	Glycerol	1.26
NaCl	0.09% physiologic saline (Baxter Corporation, Toronto)	1.00
Glu	5% glucose (Hospira Healthcare corporation, Montreal)	1.02
LR	Lactated Ringer (Baxter, Mississauga, Ontario)	1.00
DIW	Deionized water	1.00
DGW	Degassed deionized water	1.00
DGC	Degassed 30% contrast (4.5 mL of Conray 43 and 10.5 mL of 0.09% physiologic saline)	1.07
DGHPU	Degassed human pooled urine	1.01–1.02
AU1.07	Artificial urine pH 6.5	1.07
WB	Human whole blood	1.05–1.06

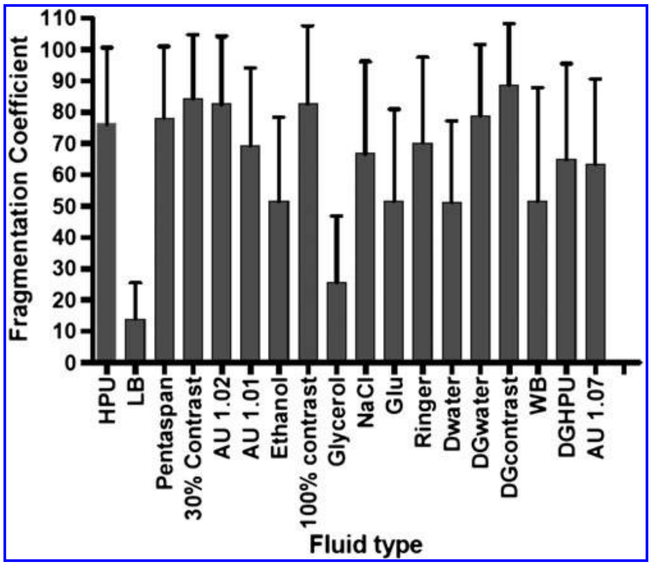

FIG. 1. Overall (narrow focus + wide focus) fragmentation coefficients of artificial stones using different fluids. Each bar represents 30 stones and error bars represent standard error. HPU = human pooled urine; AU = artificial urine; NaCl = saline; Glu = glucose; DG = degassed; WB = whole blood.

Table 2. Fragmentation Coefficients of Test Fluids

Fluid type	*Mean FC narrow focus*	*Mean FC wide focus*
AU 1.01 (control)	62.4	76.4
HPU	77.9	74.4
Lubricating jelly	14.2[a]	13.6[a]
Pentastarch	84.3	71.7
30% contrast	88.9	79.4
AU 1.02	80.8	84.1
Ethanol	47.1	55.9
100% contrast	88.5	76.5
Glycerol	17.1[a]	34.4[a]
Normal saline 0.09%	76.8	56.7
Glucose 5%	61.9	41.3[a]
Ringer lactate	56.4	84
Deionized water	43.9	58.5
Degassed deionized water	90.3	67.1
Degassed 30% contrast	95.3[b]	81.6
Degassed HPU	76.6	58.2
AU 1.07	69.5	57.2
Human whole blood	45.7	58.2

Analysis performed with Kruskal-Wallis test with the Dunn post-test.
[a]Significantly decreased.
[b]Significantly increased.
FC = fragmentation coefficient; AU = artificial urine; HPU = human pooled urine.

6/15 stones. There was a trend toward significance when compared with the control ($P = 0.08$), no difference in 6 of the groups, and significant enhancement in the other 10. Results are further summarized in Table 3.

Discussion

Despite numerous technologic advances, the clinical outcomes with SWL have not kept up with the evolution of the device and, in fact, fragmentation rates have dropped below those of the initial generation of machines. Even after multiple efforts to improve stone treatment efficacy with the newer SWL devices, the Dornier HM-3 remains the gold standard for stone-free rates.[10]

The manipulation of the fluid environment surrounding the stone to increase comminution remains a relatively unexplored strategy, and data on the effects of different fluids are very limited in the literature. Li and colleagues[7] described their experience with two types of AU (1.003 and 1.040) and two radiographic contrast concentrations (50% and 100%), finding no significant differences among the groups.

Our data show that different fluid media can have an important impact in the FC of *in vitro* SWL. While LJ (NF and WF), Gly (NF and WF), and Glu (WF) significantly decreased the FC, the use of a degassed mixture of 0.09% physiologic saline and iothalamate meglumine (Conray 43) in NF had quite the opposite effect, significantly enhancing stone fragmentation.

Furthermore, when we compared the number of completely fragmented stones, a parameter that may have more clinical importance, the use of degassed 30% contrast (DGC) clearly showed an advantage over all AU and HPU groups, and a trend toward significance when compared with the normal 30% contrast (C) and the $DGdH_2O$.

The role of SG in stone fragmentation is controversial. In our study, we tested the effect of SG by including at least nine fluids across the spectrum of physiologic and nonphysiologic SG (0.789–1.26). Focusing on the AU groups, there is an increase in fragmentation as SG increases from 1.01 (control) to 1.02 and then dropping again at 1.07 (NF and WF), although this was not significantly different. In the rest of the groups, excluding the fluids with extreme viscosity or degassing (LJ, Gly WB, $DGdH_2O$, and DGC), FC was not significantly altered by SG. Low SG also had no significant impact on FC (eg, EtOH and dH_2O), and the significant increase in FC that was seen in the DGC group is probably also not from the SG because the AU group with an identical SG did not show a significant change. In addition, the significant decrease caused by Glu (SG 1.02) but not AU 1.02 in the WF, again suggests that SG plays a minor, if any, role in stone fragmentation.

Our finding that fluid viscosity decreases FC (LJ and Gly) is concordant with previous reports, which have shown that high density fluids such as castor oil[5] and Gly[6] decrease stone comminution. Lifshitz and coworkers,[11] measuring cavitation damage in aluminum foil strips, demonstrated that another viscous medium (blood) caused less damage from its inhibition of acoustic cavitation mechanisms, a phenomenon also corroborated by our data. In an attempt to test a fluid with low viscosity (and low SG), we tested 100% EtOH. This fluid had no significant impact on the FC.

Radiographic contrast has been previously shown to induce an increase in the amplitude and frequency of cavitation occurrence.[12] We found that the use of a degassed contrast/physiologic saline (30:70 ratio) mixture significantly enhanced FC (mean 88.5% and 95.3%, overall and NF, respectively). This was an unexpected finding, especially because our 30% and 100% groups and a 50% contrast group reported by Li and colleagues[7] did not show a difference compared with controls. In an effort to further improve the FC

Table 3. Phantoms Reaching Complete Fragmentation (Fragmentation Coefficient 100%) by Type of Fluid

Fluid type	*SG*	*Number CF (%) NF*	P *value*[a]	*Number CF (%) WF*	P *value*[a]
AU 1.01 (control)	1.01	2 (13.3)	0.0007	1 (6.6)	0.08
HPU		5 (33.3)	0.02	1 (6.6)	0.08
Lubricating jelly	1.015	1 (6.6)	0.0001	0 (0)	0.01
Pentastarch	1.01	5 (33.3)	0.02	0 (0)	0.01
30% contrast	1.07	6 (40)	0.06	3 (20)	0.24
AU 1.02	1.02	3 (20)	0.002	0 (0)	0.01
Ethanol	0.789	0 (0)	0.0001	0 (0)	0.01
100% contrast	1.22	5 (33.3)	0.02	4 (26.6)	0.69
Glycerol	1.26	0 (0)	0.0001	0 (0)	0.01
Physiologic saline 0.09%	1.00	2 (13.3)	0.0007	0 (0)	0.01
Glucose 5%	1.02	0 (0)	0.0001	0 (0)	0.01
Ringer lactate	1.00	0 (0)	0.0001	2 (13.3)	0.11
Deionized water	1.00	0 (0)	0.0001	0 (0)	0.01
Degassed deionized water	1.00	6 (40)	0.06	0 (0)	0.01
Degassed 30% contrast	1.07	12 (80)		6 (40)	
Degassed HPU		4 (26.6)	0.009	0 (0)	0.01
AU 1.07	1.07	2 (13.3)	0.0007	1 (6.6)	0.08
Human whole blood	1.06	1 (6.6)	0.02	0 (0)	0.01

Analysis performed with Chi square.
[a]*P* value obtained when comparing degassed 30% contrast mixture.
SG = specific gravity; CF = complete fragmentation; NF = narrow focus; WF = wide focus; AU = artificial urine; HPU = human pooled urine.

of the 30%C, we degassed this medium. When the number of completed fragmented phantoms were compared, DGC was significantly better than the control ($P = 0.007$), and there was a trend toward significance when compared with the standard 30% C and $DGdH_2O$ groups. This CF end point might turn out to be the most relevant to the clinician, because it represents the best chance of reaching a stone-free status in a SWL-treated patient.

Using degassed water as a cavitation promoting agent has been reported previously by Zhu and associates[5] and Pishchalnikov and coworkers,[4] and the only other use of other degassed fluids reported to our knowledge has been Ringer buffer.[11]

Another important finding was the wide dispersion of FC across all of the fluid groups. One hypothesis to explain this variability is the fact that cavitation and SW damage are not precisely repeatable from SW to SW.[4] The concern that stone phantoms could be the source of this variability by containing gas pockets or cement nuclei, making them either abnormally harder or softer, was addressed by randomly sampling some of our phantoms with cross-sectional CT. The absence of any heterogeneity in the phantoms and further analysis showing no difference in the FC produced from phantoms with high *vs* low HU values would seem to refute that concern. Furthermore the overall mean HU of the evaluated phantoms was 1793 HU, which is well above the 900 HU reported for SWL resistant stones.[13]

We must acknowledge several weaknesses of our test design. Although we tested a large number of phantoms, the number in each group was limited, leading to the potential of a type II error in some fluid groups. Our definition of the percentage of fragmentation is based on a larger fragment diameter (<4 mm) than that of previously reported trials, although it is still within the range of spontaneous passage by a patient. The selection of AU SG 1.01 as our urine control was made to represent a hypothetical well-hydrated healthy person.[14] The SG of a fasting patient undergoing SWL may be closer to SG 1.03 [15] or higher, depending on their fasting time, previous hydration status, and treatment fluid replacement. To our knowledge, however, there are no data on the urine SG of subjects while undergoing SWL or immediately after. Although we tested a HPU group, we decided against using it as the control, because of the high variation in urine parameters of the batches and potential for introducing other confounding factors from the urine donor.

The strengths of this study include that it was carried out on the newest generation of lithotripter, and thus these results may be more applicable than others that were obtained previously from the HM-3 machine. All tests were performed using a standardized protocol with a tissue model that accurately simulates SW dampening.

Our data, if further validated in an *in vivo* setting, could justify future clinical trials aimed at the manipulation of a patient's urinary tract fluid environment to enhance stone fragmentation rates either via intravenous or retrograde fluid injection.

Conclusion

We have shown that the *in vitro* FC of test phantoms is modifiable by using different fluid mediums. The role of SG in stone fragmentation could not be supported by our data. The use of a degassed 30% contrast significantly increased the stone fragmentation rate and number of completely fragmented phantoms.

Disclosure Statement

No competing financial interests exist.

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Abbreviations Used

AU = artificial urine
C = contrast
CF = complete fragmentation
CT = computed tomography
DG = degassed
DGC = degassed 30% contrast
dH_2O = deionized water
EtOH = ethanol
FC = fragmentation coefficient
Gly = glycerol
Glu = glucose
HPU = human pooled urine
HU = Hounsfield unit
LJ = lubricating jelly
NF = narrow focus
SG = specific gravity
SW = shockwave
SWL = shockwave lithotripsy
30%C = 30% contrast
WB = whole blood
WF = wide focus