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RANDOMIZED CONTROLLED TRIAL COMPARING THREE DIFFERENT MODALITIES OF LITHOTRITES FOR INTRACORPOREAL LITHOTRIPSY IN PCNL

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Abstract

Purpose: To compare the efficiency (stone fragmentation and removal time) and complications of three models of intracorporeal lithotripters in percutaneous nephrolithotomy (PCNL).

Materials and Methods: Prospective, randomized controlled trial at nine centers in the North America from 2009 to 2016. Patients were randomized to one of three lithotripter devices: the Cyberwand, a dual probe ultrasonic device; the Swiss Lithoclast Select, a combination pneumatic and ultrasonic device; and the StoneBreaker, a portable pneumatic device powered by CO_2 cartridges. Since the StoneBreaker lacks an ultrasonic component, it was used with the LUS-II ultrasonic lithotripter to allow fair comparison with combination devices.

Results: 270 patients were enrolled, 69 were excluded after randomization. 201 patients completed the study: 71 in the Cyberwand group, 66 in the Lithoclast Select, and 64 in the StoneBreaker group. The baseline patient characteristics of the three groups were similar. Mean stone surface area was smaller in the StoneBreaker group at 407.8mm^2 vs 577.5mm^2 (Lithoclast Select) and 627.9mm^2 (Cyberwand). The stone clearance rate was slowest in the StoneBreaker group at 24.0 mm^2/min vs 28.9 mm^2/min and 32.3 mm^2/min in the Lithoclast Select and Cyberwand groups respectively. After statistically adjusting for the smaller mean stone size in the StoneBreaker group, there was no difference in the stone clearance rate among the three groups (p=0.249). Secondary outcomes, including complications and stone free rates, were similar between the groups.

Conclusions: The Cyberwand, Lithoclast Select, and the StoneBreaker lithotripters have similar adjusted stone clearance rates in PCNL for stones > 2cm. The safety and efficacy of these devices are comparable.

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Introduction

Percutaneous nephrolithotomy (PCNL) is the preferred treatment modality for renal stones greater than 2 cm in diameter, including staghorn calculi (1). PCNL success rates, defined as patients rendered stone free on post-operative imaging, range from 75-90% (2-4).

The efficiency of the intracorporeal lithotripter device, the instrument used to remove the majority of the stone burden, is essential to successful stone clearance. For decades ultrasonic devices have been a mainstay of percutaneous stone removal, utilizing reusable probes thus minimizing disposable costs. More recently, manufacturers have introduced intracorporeal lithotripters to fragment stones with a variety of energy sources, including pneumatic, ultrasonic, and combination modalities. All of these newer devices utilize disposable probes. Each device features unique properties designed to improve the efficiency of stone clearance, yet few randomized comparison studies have been performed to assess the validity of such claims (5).

Prior studies comparing lithotripter models have yielded variable results. We sought to compare the efficiency (stone fragmentation and removal time) of three current generation lithotripters: the Cyberwand (ACMI/Olympus, Center Valley, PA), a dual probe ultrasonic device; the Lithoclast Select (Boston Scientific, Marlborough, MA), a combination pneumatic/ultrasonic device; and the StoneBreaker™ (Cook Medical, Bloomington, IN), a portable pneumatic device powered by CO_2 cartridges. Since the StoneBreaker lacks an ultrasonic component, it was combined with the LUS-II ultrasonic lithotripter to allow fair comparison with other devices. If a particular device offered superior stone clearance, this would help inform equipment utilization decisions.

Materials and methods

Study design and participants

We conducted a prospective, multicenter, randomized, controlled trial with nine participating sites across North America (Table 1). Each site obtained ethics approval from their respective institutional review board (IRB). Study analysis and data management

were conducted at Indiana University (IRB approval number 1010002258). The study was registered in the ClinicalTrials.gov database **(**NCT00952315). Subjects meeting inclusion criteria were invited to participate after obtaining patient consent. Inclusion criteria are detailed in Table 2. In particular, only patients undergoing PCNL with target stone size greater than 2cm were enrolled in this study.

Randomization

Subjects were randomized to one of the three devices (Cyberwand, StoneBreaker, or Lithoclast Select) by the research coordinator at the central study site (Indiana University) to minimize allocation error and potential selection bias. Investigating sites contacted the lead site to obtain the randomization result for each patient as they were accrued. Subjects were assigned to study groups using a permuted-block randomization schedule developed by a biostatistician. This method was employed to ensure that the number of subjects assigned to each group was reasonably balanced throughout the study. A randomization log was maintained.

Procedures

Stone surface area (mm^2) of the target stone was measured on pre-operative computed tomography (CT) scan or kidneys, ureter, bladder (KUB) x-ray by the lead investigator at each study site. The shape of the target stone was outlined allowing standard radiology viewing software to calculate the surface area. This method has been previously shown to give excellent correlation to stone volume (6). The percutaneous access was established by a urologist, in a prone position and the target stone was visualized. The time (mins) taken to clear the target stone was recorded by designated study personnel using a stopwatch. Clearance time included time spent using the graspers or basket to remove target stone fragments but not pauses to replace broken probe, unclog the probe, or attend to patient care issues. Only the time taken to treat the target stone (typically the largest stone in the kidney) was measured. If other stones were present, they were subsequently treated but not included in the study. The Lithoclast Ultra was used with both ultrasound and pneumatic components. Since the StoneBreaker is unable to remove the stone fragments it creates, it was used in combination with the ultrasonic Olympus

LUS-II (Olympus, Melville, NY) lithotripter in this trial. The LUS-II was used only after stone fragmentation by the StoneBreaker was achieved and larger pieces were already removed using graspers. It was used primarily to suction up smaller fragments rather than to fragment the main stone. Clearance rate was calculated by dividing the surface area of the targeted stone (mm^2) by the total clearance time (min). Other study parameters including number and location of accesses, anesthesia type, blood loss, drainage type, length of stay, transfusion rates, secondary procedures, and complications were also recorded. Stone free rate (a secondary study outcome) was defined as no visible fragments. It was determined either by visualization at secondary nephroscopy or a CT scan within 30 days of the initial procedure. Secondary nephroscopy was employed as a surrogate of stone free rate since only patients who harbor residual stones on postoperative imaging (typically a CT scan) would be offered this procedure. Stone composition was recorded as the predominant component on stone analysis. Except for the use of a specific lithotripter they were randomized to, the management of the patients in this trial did not otherwise differ from the standard PCNL operation.

Outcomes

The primary study outcome was target stone clearance time in minutes. Stone size variability was larger than expected so an additional outcome of clearance rate (mm^2/min) was added. To calculate stone clearance rate, the target stone surface area was divided by the stone clearance time. Secondary outcomes were stone free rate (assessed as described above), secondary procedures rate, complications, and length of stay.

Statistical analysis

Sample size calculations were performed by a biostatistician using a two-sided, two-sample Student t-test. Since comparisons were made between all three treatment groups, the significance level used to determine the sample size was adjusted. For simplicity, the Bonferroni method was employed (i.e. $\alpha = 0.05/3 = 0.017$). The primary outcome of interest was the stone clearance time (min). From previous experience in a similar study at our institution, the mean clearance time for stones between 500 mm^3 and 1000 mm^3 using the Olympus LUS-II was found to be 13.7 ± 6.0 minutes. Similar results were

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expected in our trial. Assuming one of the other study groups has a true stone clearance time that is 25% different than the Olympus LUS-II, then 70 subjects in each group were required to provide 82% power to detect that difference. A total of 210 subjects were needed, 70 into each treatment group. Each arm of the study could enroll up to 90 subjects for a total of up to 270 subjects across all sites to obtain 210 completed subjects. Each individual site was allowed to enroll up to 75 subjects.

Statistical analysis was performed using Minitab 14.2 Statistical Software. Minitab, Inc., State College, PA (www.minitab.com) and R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna Austria. (http://www.R-project.org/). All subject demographics were summarized by experimental group using descriptive statistics and tabulated. Continuous demographic variables were compared across study groups using analysis of variance (ANOVA). Categorical demographic variables were compared using Pearson Chi-square tests. The mean stone clearance time was determined for each experimental group. Mean times were compared across groups using ANOVA. To investigate pairwise differences between individual groups, Tukey's HSD post hoc test was used. Continuous measures were summarized using mean (standard deviation, SD) or median (min, max) and compared across groups using ANOVA. Categorical measures were summarized using frequency (percent) and compared across groups using Fisher's Exact test.

Results

A total of 270 patients were enrolled and randomized at 9 sites from October of 2009 to February of 2016. Patient enrolment by site is detailed in Figure 1. After randomization, 69 patients were excluded. The reasons for exclusion post randomization by treatment group are detailed in Figure 2. The most common exclusion reasons were: device not used (17/69 patients, 25%), data not available (16/69, 23%), absence of signed consent form (12/69, 17%), and inability to access the stone (10/69, 14%). The study was completed by 201 patients, 71 in the Cyberwand group, 66 in the Lithoclast Select, and 64 in the StoneBreaker. The study outline is detailed in Figure 3.

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The mean patient age was 57 years (range 20-89 years) and 104/201 (52%) were female. Patients were well matched on baseline characteristics in the three treatment groups, as detailed in Table 3. However, the stone surface area was significantly lower in the StoneBreaker group at 407.8 mm^2 compared to 627.9 mm^2 in the Cyberwand and 577.5 mm^2 in the Lithoclast Select groups respectively (p=0.005). The stone clearance time did not differ significantly between the three comparison groups at 28.9 min (Cyberwand) vs 26.6 min (Lithoclast Select) and 23.4 min (StoneBreaker) (p=0.473). The stone clearance rate (stone surface area divided by the total clearance time) varied from 24.0 mm^2/min in StoneBreaker group to 28.9 mm^2/min in Lithoclast Select and 32.3 mm^2/min in the Cyberwand group, making the Cyberwand appear to be the most effective (p=0.036). As the stone clearance rate could be affected by stone size, analysis of covariance (ANCOVA) was used to compare the rates across groups while adjusting for stone size. After adjusting for smaller average stone size in the StoneBreaker cohort, there was no significant difference in stone clearance rates between the three devices (p=0.249, Table 4).

Secondary outcomes, including intra-operative or post-operative complications and stone free rates were similar between the groups. There were no statistically significant differences in the rates of stent placement, nephrostomy tube placement, use of other devices, reported intraoperative complications, estimated blood loss (EBL) > 400ml, red blood cell (RBC) transfusion rates, and the average length of stay. Of the intraoperative complications reported, bleeding (6 patients, 3%) and collecting system perforation (7 patients, 3.5%) were the most common. Post-operatively, fever (6 patients, 3%), pleural effusion or pneumothorax (5 patients, 2.5%), and sepsis (3 patients, 1.5%) were the most commonly reported complication. Secondary outcomes are further detailed in Table 5. The stone free rate following the primary PCNL procedure, defined as no visible stones on post-operative CT scan, averaged 58% with no significant difference between the three groups (p=0.277). Stone composition was similar in the three groups. The clearance rate of “hard” stones (defined as brushite, cystine, and uric acid stones) was comparable across the 3 groups: 25.7 mm^2/min in the Cyberwand group, 24.0 mm^2/min in the Lithoclast group, and 20.1 mm^2/min in the StoneBreaker group (p=0.671).

Discussion

Lithotripter efficiency is a crucial component of a rapid and successful PCNL procedure. We studied three modern lithotripters to determine stone clearance efficiency in a clinical setting using a randomized controlled trial design to minimize the risk of bias. To allow for fair comparison of devices, StoneBreaker was used in combination with an ultrasonic lithotripter (LUS-II) since the StoneBreaker lacks ultrasonic capability of its own. We included time spent retrieving target stone fragments in the overall treatment time to ensure assessment of true stone clearance and not just the fragmentation time alone. While there appeared to be differences in the clearance rate between groups, after taking into account the variation in stone sizes between groups, we did not find a statistically significant difference between the three devices. The study demonstrated equivalent safety and efficacy of the three devices. There were no significant differences in stone free status and intra-operative or post-operative complications. Our findings should be taken into account when considering the purchase of costly lithotripter equipment. Since the device efficiency, as assessed by stone clearance rates, is similar, other factors become more important in choosing a specific lithotripter device. These factors include ergonomics, durability, cost of disposable pieces, and contracts with vendors (Table 6). For example, a strategy to reduce cost might be to use an ultrasonic device such as LUS-2 lithotripter initially (reusable parts) for the majority of stones, with the addition of the StoneBreaker for pneumatic fragmentation of particularly hard stones only. In most situations, this would eliminate the need for the routine use of expensive disposables. Some of the advantages and disadvantages of the three devices are outlined in Table 7.

Previous studies have compared several lithotripters. Krambeck et al found no difference in stone clearance rate between the Olympus LUS-II and Cyberwand lithotripters in a randomized trial (7). In another trial, Chew et al found StoneBreaker to be superior to the Swiss Lithoclast (8). The Lithoclast Ultra was found to be significantly faster than the LUS-II in a study by Pietrow et al (9). El-Nahas et al compared an ultrasonic lithotripter (Calcuson/Endomat by Karl Storz) with the holmium laser lithotripsy noting comparable efficacy (10). Radfar et al found comparable stone clearance with the EMS Swiss LithoClast and EMS Swiss lithotripter (11). We incorporated nine high volume sites across North

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America to make this study the largest randomized controlled trial to date on this subject and the first comparing Cyberwand, Lithoclast Select, and the StoneBreaker directly. The outcomes we report may not be reproducible in a lower volume, smaller center without the same operating room resources and staff experience in lithotripsy.

One unexpected finding in our study is the significantly smaller mean stone surface area in the StoneBreaker group. This result is difficult to explain as our study protocol included randomization, thereby controlling for the stone size variable. We carefully reviewed our primary data to identify possible reasons for this finding. Study authors checked individual patient data with regard to stone size. No obvious systemic data entry error existed to explain the smaller stone size in StoneBreaker group. The patients were randomized from a central location making bias from one of the treatment sites to use a particular device for smaller stones unlikely. The reasons for patient exclusion after randomization were similar across the three study groups (Figure 4). Given the smaller average stone size in the StoneBreaker group, statistical adjustments were necessary to compare efficacy of treatment. We used analysis of covariance (ANCOVA) to adjust for stone size and found no significant difference in clearance rate between the three groups (p=0.249, Table 4). Despite the differences in average surface area, we feel this adjustment would make for a fair comparison between the devices.

Another limitation of our study is that it is slightly underpowered. A total of 201 patients, with 71, 66, and 64 patients in the Cyberwand, Lithoclast Select, and StoneBreaker treatment groups respectively, completed the study. Our study was powered for 70 patients in each arm. To allow for possible exclusions, 270 patients were randomized. Slightly more than anticipated patients were excluded after randomization resulting in marginally underpowered study. As detailed in Table 4, clearance time and adjusted clearance rate were not significantly different between the treatment groups. It is possible (but unlikely) that the underpowered sample size is responsible for the finding of no difference between the study groups. A larger target stone size might also have helped differentiate lithotripters, albeit at the expense of reduced study participant numbers.

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Conclusions

This large, multicenter, randomized, controlled trial compared three commonly utilized lithotripter devices. Although the StoneBreaker appeared to have a slower clearance rate, this may be due to a smaller average stone size in that group. When adjusted for the difference in stone size between groups, the Cyberwand, Lithoclast Select, and the StoneBreaker (in combination with ultrasonic LUS-II) lithotripters have similar stone clearance rates during PCNL for stones greater than 2cm. The safety and efficacy of these devices are comparable.

Funding

Cook Medical (StoneBreaker), Boston Scientific Corporation (Lithoclast Select), and ACMI/Olympus (Cyberwand) supplied the lithotripsy test equipment to each study site. No company funding was utilized for study analysis and result reporting.

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Abbreviations

PCNL	Percutaneous nephrolithotomy
IRB	Institutional Review Board
CT	Computed tomography
KUB	Kidneys, ureter, bladder
ANOVA	Analysis of variance
SD	Standard deviation
ANCOVA	Analysis of covariance
EBL	Estimated blood loss
RBC	Red blood cell
UTI	Urinary tract infection

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Table 1: Study sites and primary investigators

Site	Primary Investigator
Indiana University	James Lingeman
University of British Columbia	Ben Chew and Ryan Paterson
Western University	John Denstedt and Hassan Razvi
Northwestern University	Robert Nadler
Mayo Clinic Arizona	Mitchell Humphreys
Duke University	Glenn Preminger
University of Wisconsin	Steven Nakada
Mayo Clinic Rochester	Amy Krambeck
Vanderbilt University	Nicole Miller

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Table 2: Study inclusion and exclusion criteria

Inclusion	**Exclusion**
Undergoing PCNL	Pregnancy
Stone size > 2 cm in at least one dimension	Stone < 2 cm size in each dimension
Able to measure stone on CT/KUB X-ray	Active urinary tract infection
>18 years old	SWL in the last 3 months
Able to consent	Complex stone requiring multiple access sites
	Unable to measure stone

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Table 3: Baseline patient characteristics

	Cyberwand n=71	**Lithoclast Select n=66**	**StoneBreaker n=64**	**p-value**
Age (years)	57.4	58.1	55.2	0.481
Gender (female)	54%	52%	50%	0.921
Mean ASA	2.5	2.4	2.4	0.881
BMI	30.4	31.3	30.1	0.666
Pre-operative hemoglobin	13.3	13.8	13.9	0.171
Pre-op creatinine mg/dl	1.0	1.0	1.0	0.966
Previous surgical treatment for stones	45.6%	35.4%	48.4%	0.289

Table 4: Stone clearance rates by treatment group

	Cyberwand n=71	**Lithoclast Select n=66**	**StoneBreaker n=64**	**p-value**
Stone surface area in mm^2, (SD)	627.9 (516.8)	577.5 (399.8)	407.8 (216.6)	**0.005**
Procedure time in mins, (SD)	152.2 (61.4)	146.5 (72.1)	129.8 (45.2)	0.109
Clearance time in mins, (SD)	28.9 (29.9)	26.6 (26.9)	23.4 (20.3)	0.473
Clearance rate in mm^2/mins, (SD)	32.3 (23.4)	28.9 (16.2)	24.0 (13.9)	0.036
Adjusted clearance rate in mm2/min	31.1	28.5	25.9	0.249

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Table 5: Secondary outcomes by treatment group

	Cyberwand n=71	Lithoclast Select n=66	StoneBreaker n=64	p-value
Ureteral stent placed	5 (7.0%)	4 (6.1%)	3 (4.7%)	0.932
Nephrostomy tube placed	63 (90.0%)	59 (90.8%)	55 (88.7%)	0.956
Use of other device	5 (7.3%)	9 (14.8%)	8 (13.3%)	0.369
Intra-operative complication	11 (16.7%)	5 (7.8%)	11 (17.5%)	0.205
EBL >400cc	3 (4.4%)	2 (3.1%)	4 (6.7%)	0.637
RBC transfusion	2 (2.9%)	2 (3.0%)	3 (4.7%)	0.799
Length of stay (days)	2.6 (2.5)	2.5 (2.1)	1.9 (1.5)	0.127
Post-operative complications	11 (16.2%)	10 (15.2%)	10 (15.9%)	1.0
Stone free after first procedure	39 (56.5%)	43 (65.2%)	33 (51.6%)	0.277
Secondary procedure required	24 (35.8%)	16 (25.4%)	15 (23.8%)	0.279

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Table 6: Pros and cons of study devices

Device	Advantages	Disadvantages
Cyberwand	• All-in-one probe • Able to both fragment and remove stone	• Noisy • Heavy • Small suction probe diameter • Disposable probe costs
Lithoclast Select	• Optional pneumatic component • Able to both fragment and remove stone	• Prone to clogging due to smaller probe lumen • Large size of the device • Heavy • Ultrasound probe prone to overheating – should be used at 40-70% of power only[9] • Disposable probe costs
StoneBreaker	• Portable, no cables required • Ergonomic design • Lightweight • Probe causes minimal tissue trauma	• Requires separate method for fragment removal (grasper or ultrasonic lithotriptor) • Disposable probe costs

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FIGURE LEGENDS

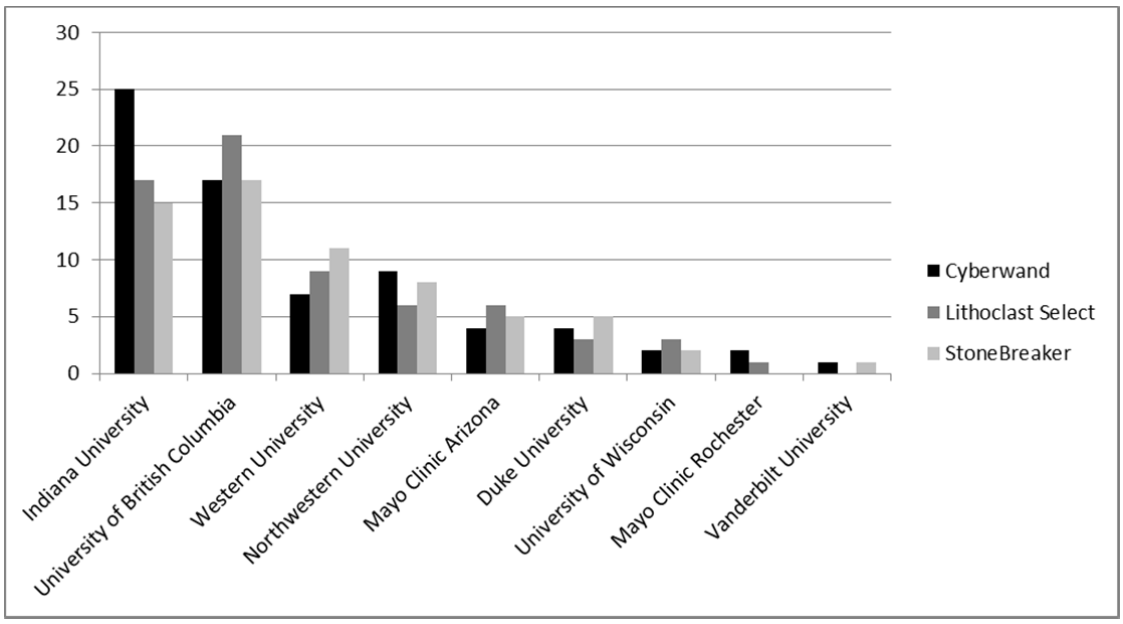

Figure 1: Patient enrollment by study site

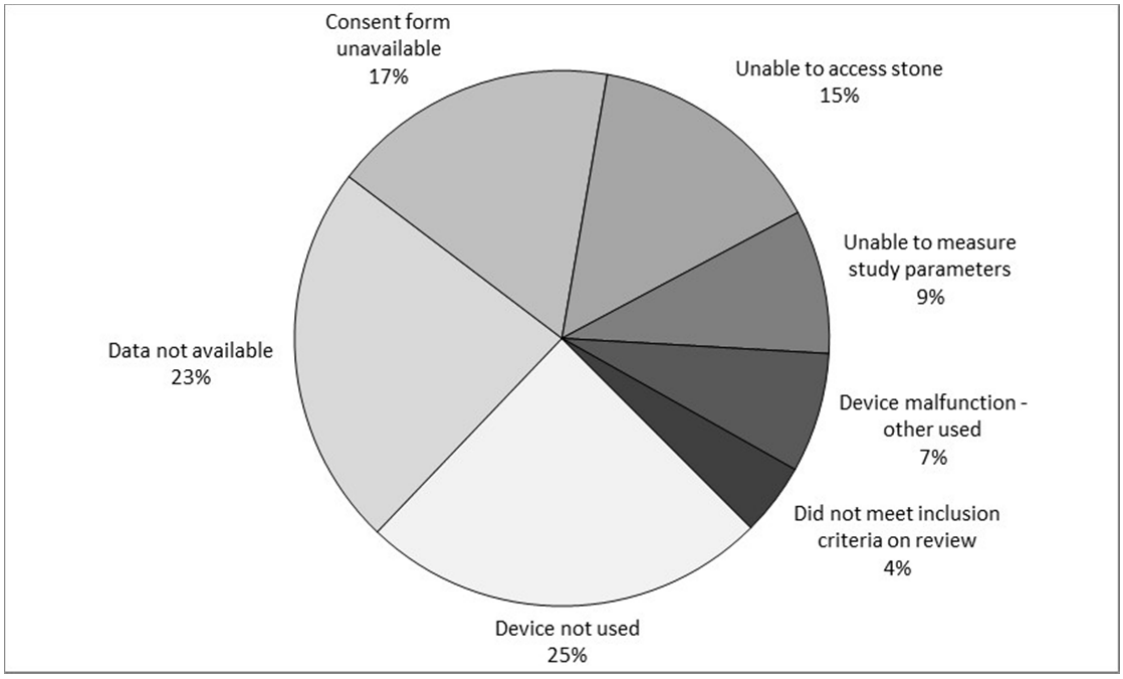

Figure 2: Reasons for patient exclusion (n=69)

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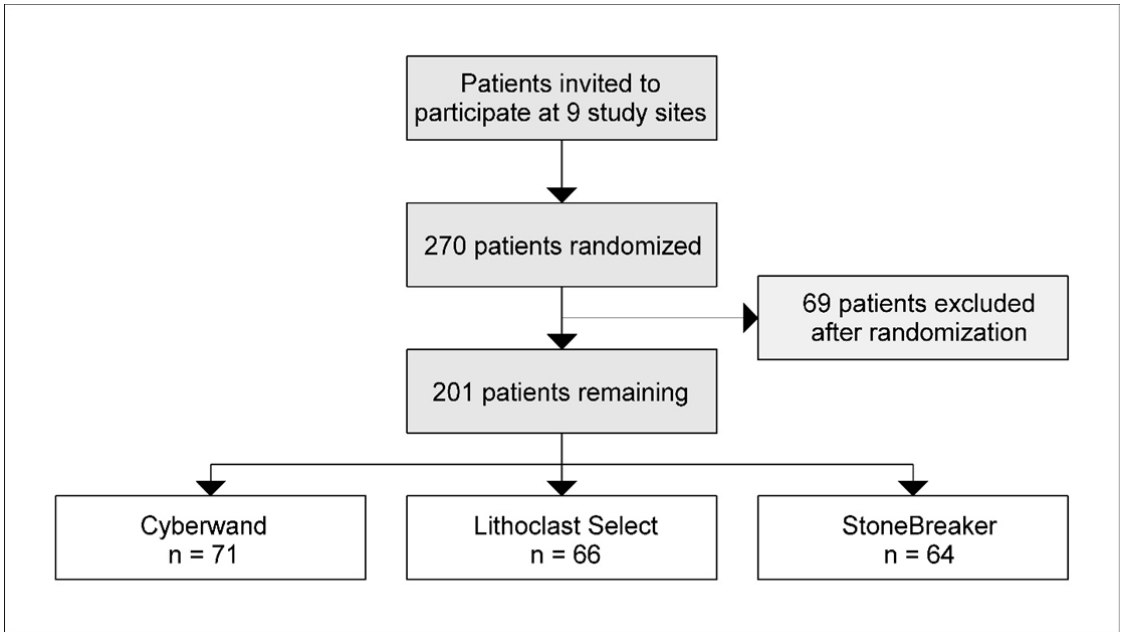

Figure 3: Study outline

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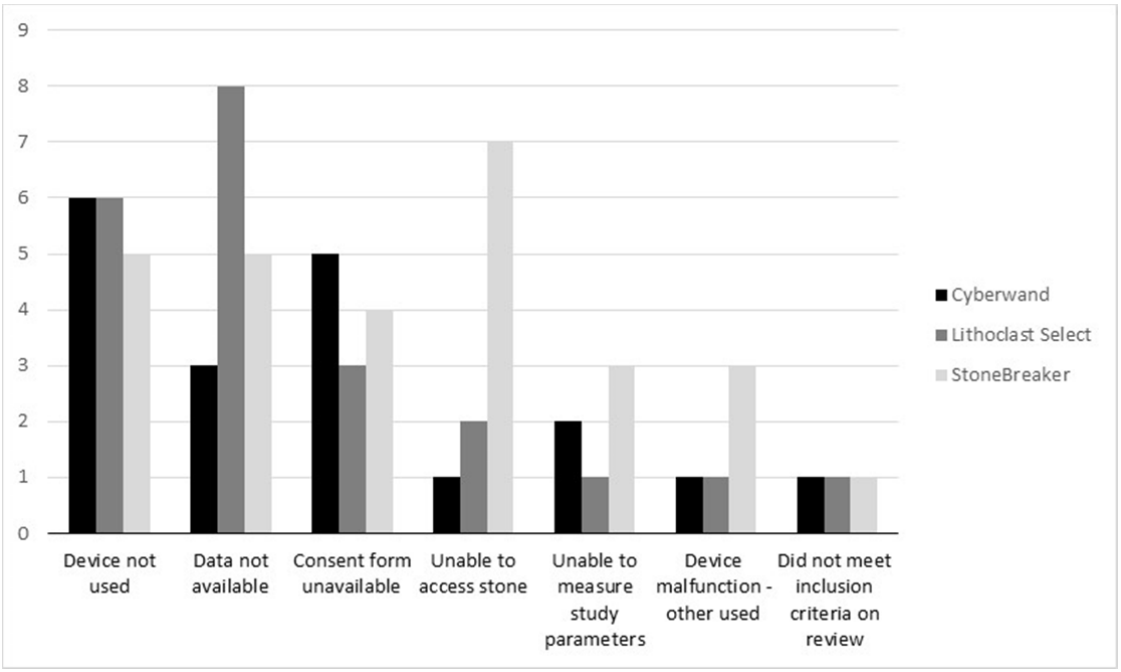

Figure 4: Excluded patients by treatment group

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