E3000 Clinical Study Synopsis

Study Design

Medispec Ltd. (USA) conducted a multi-center clinical trial to determine the safety and effectiveness of the Medispec Lithotripter in the non-invasive fragmentation of upper urinary tract calculi between 5 and 20 mm in size. These investigations were conducted at four sites in the United States, with a total of 181 patients.

The objective of the study was to determine the safety and success rates of fragmentation of stones treated with the Medispec Lithotripter.

Radiologists evaluated the patient's radiographs for stone status, including size and location. The results were compared to those obtained in similar patients who underwent treatment with currently legally marketed lithotripters as reported in the literature.

Male or female patients older than 18 years of age with upper urinary tract stones were eligible for enrollment in the study. All patients were to have at least one stone greater than or equal to 5 mm and no stone larger than 20 mm; were to be classified as anesthesia risks I, II, III, or IV; were to have negative urine culture for bacteria; and were to have given informed consent. Patients were excluded from the study if their anatomy prevented focusing of the device; if they had renal artery calcification in the treatment area; if they had lower or middle urinary tract stones or obstructions distal to the target stone; if epidural or general anesthesia was contraindicated; if exposure to radiation was not advisable (e.g., pregnancy); if they had a coagulation abnormality or were receiving drug therapy that may affect coagulation, including aspirin; if they had a cardiac pacemaker or other implanted device; or if they were known to have struvite or cystine stones.

A thorough history and physical examination was conducted prior to treatment. Follow-up tests, including anatomical and functional kidney evaluations, were performed on each patient at 2 weeks, 30 days, and 90 days following treatment or until the patient exited the study. Success was defined as fragmentation of the targeted stone into pieces < 5 mm in their largest dimension. A patient could exit the study when he or she had completed the 90-day follow-up period or at any time it was determined that he/she was free of the target stone or had residual fragments of that stone measuring < 5 mm in diameter.

Study Population

Of the 181 patients enrolled in the study, 121 were male and 60 were female. Patient age ranged from 22 to 82 years, with a mean of 51 years. Patient's weight varied widely, ranging from 113 lbs. to 296 lbs. with a mean of 186 lbs. Of the 181 patients enrolled in this study, 47% had a history of kidney stone disease.

The treated stones ranged in size from 4 mm to 22 mm in largest diameter. However, data analysis was performed only on stones, which were in the 5 to 20 mm range (186 targeted stones), as specified in the Indications for Use section. The mean stone size was 9.2 mm. Of the 186 targeted stones, 106 (57.0%) were located in the calices; 35 (18.8%) were located in the renal pelvis. Forty-five of the 186 target stones (24.2%) were originally located in the ureter, 7 of which were pushed into the renal pelvis with a stent immediately prior to treatment.

Of the 181 patients enrolled, 180 patients received 192 treatments. An average of 1936 shocks was delivered per treatment.

Safety

The adverse effects in Table 1 below were observed during the study. The occurrence is cited for the total cohort[1] in the study.

Table 1 - Numbers of Adverse Events During the Clinical Study

(Immediate Post-Op n=Total # of Treatments; 2 Weeks & 3 Months Post-Op n=Total # of Patients at Visit)

Adverse Event	Immediate Post-Op (n=211 txs.)	2 Weeks Post-Op (n=174 pts.)	3 Months Post-Op (n=76 pts.)
Bruising/Redness	160	13	0
Hematuria	144	24	4
Renal Colic/Flank Pain	63	15	5
Nausea/Vomiting	49	2	0
Muscle/General Pain	43	6	0
Dysuria	7	8	4
UTI	2	7	1
Urosepsis	1	2	1
Total Ureteral Obstruction	0	2	1
Sustained Arrhythmia's	0		
Sustained Hypertension	10 (n=159 pts.)		

1. Bruising or redness at the treatment site, which has been reported by most of the manufacturers of Lithotripsy devices, was observed in 13 (7.5%) of the 174 total patient cohort treated with the Medispec Lithotripter at the two-week visit. Bruising and redness had disappeared at the three-month visit.

2. Hematuria, defined as the presence of blood in the urine which can be seen with the naked eye, was observed in 24 (13.8%) of the 174 patient cohort treated with the Medispec Lithotripter at the two week visit and in 4 out of 76 patients (5.3%) at the three month visit.

3. Renal Colic/Flank Pain, caused by distension of the ureter by a stone or stone fragment, was observed in 15 (8.6%) of the 174 total patient cohort treated with the Medispec Lithotripter at the two week visit and in 5 out of 76 patients (6.6%) at the three month visit.

[1] The total cohort consists of 174 patients who were treated with stones sizes in the evaluable range of 5-20 mm.

4. Nausea and Vomiting, ranging from mild nausea to severe vomiting requiring hospitalization is a common adverse effect of Lithotripsy. Of the 174 total patient cohort treated with the Medispec Lithotripter, 2 patients (1.1%) had nausea and vomiting at the two week visit and no patients reported nausea and vomiting at the three month visit.

5. Muscle/general pain, defined as mild to moderate discomfort in the region of the shock wave entry was experienced by 6 (3.4%) of the 174 total patient cohort treated with the Medispec Lithotripter at the two week visit and no patients had muscle pain at the three month visit.

6. Dysuria, defined as difficulty or pain on urination, was observed in 8 (4.6%) of the 174 total patient cohort treated with the Medispec Lithotripter at the two week visit, and 2 out of 76 patients (5.3%) experienced dysuria at the three month visit.

7. Elevated serum amylase levels were seen in five out of 211 treatments (2.4%) immediately post-treatment. No patients had elevated amylase levels at the three-month visit.

8. Urinary Tract Infection (UTI), defined as a significant bacteriological contamination of the urinary tract, was seen in 7 (4.0%) of the 174 total patient cohort treated with the Medispec Lithotripter at the two week visit and 1 out of 76 patients (1.3%) had a urinary tract infection at the three-month visit.

9. Urosepsis, defined as a spread of microorganisms into the blood from the urinary tract, was in 2 (1.1%) of the 174 total patient cohort treated with the Medispec Lithotripter at the two week visit and 1 out of 76 patients (1.3%) had urosepsis at the three month visit.

10. Total Ureteral Obstruction, defined as complete blockage of the ureter by a stone or stone fragment, was experienced by 2 (1.1%) of the 174 total patient cohort treated with the Medispec Lithotripter at the two week visit and 1 out of 76 patients (1.3%) had a total ureteral obstruction at the three month visit.

11. Sustained arrhythmia, defined as a lasting change in the rhythm of the heart, was not observed in any of the patients treated with the Medispec Lithotripter.

12. Sustained hypertension, defined as an increase of $\geq$ 10 mm HG over pre-treatment levels at more than 1 follow-up visit, was observed in 10 (6.3%) of the 159 patients who had more than 1 follow-up visit. A detailed review of the published medical literature supports the conclusion that hypertension is not a long-term risk for extracorporeal shock wave Lithotripsy.

Effectiveness

Evaluation of the effectiveness of treatment with the Medispec Lithotripter was based on the presence and size of retained kidney stones or stone fragments 3 months post-treatment. The treatment was considered effective if on of the following criteria was met: (I) The patient was completely free of the targeted stone(s) at 3 months or less; or (II) The patient retained no fragments from the targeted stone(s) that were 5 mm or larger in the upper urinary tract.

The evaluable cohort (n = 150) excludes patients who were treated early in the study at two of the four sites. These patients had lower success rates than the overall study population. Upon retraining of the investigators at these sites, the success rates for the subsequent cases were shown to be statistically poolable.

Table 2 - Success Rate

Site	Treated	Successes	% Success
Total Cohort	186	140	75.3%
Evaluable Cohort	150	125	83.3%
Non-Calyceal Stones	75	66	88.0%
Calyceal Stones	75	59	78.7%