Extracorporeal shock wave lithotripsy – How can we further optimize its results?

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DECLARATION OF ORIGINALITY

The work contained in this thesis is original. This thesis has not been submitted for any other degree. Except for the second study, the studies described herein were carried out in the Scottish Lithotriptor Centre, Western General Hospital, Edinburgh, during my overseas training from July 2002 to June 2003, under the supervision of Mr. David Tolley. The second study was carried out in the Division of Urology, Department of Surgery, Prince of Wales Hospital, Hong Kong. I was responsible for designing and conducting all of these studies and the manuscript preparation.

ABSTRACT OF THE THESIS

Objectives

Despite the initial success of extracorporeal shock wave lithotripsy (ESWL), the performance of the contemporary machines has never been as good as that of the first-generation machine. Therefore, a series of studies was conducted to advance the current knowledge of ESWL and investigate possible ways to further optimize the treatment outcomes.

Materials and Methods

In a retrospective review of treatment information of 2192 patients, the effect of age on stone-free rates after ESWL was assessed. Next, in a prospective study, the role of stone parameter, measured using non-contrast computerized tomography (NCCT), in predicting the treatment outcomes of upper ureteric stones was examined. The general applicability of caliceal pelvic height (CPH) in determining the treatment outcomes for lower caliceal stones for three different lithotriptors was assessed in the third study. In another retrospective comparative study, the effect on treatment outcomes of additional usage of intravenous analgesic during ESWL, as compared to oral analgesic premedication alone, was analyzed. Finally, the feasibility of the use of two statistical methods, logistic regression and matched-pair analysis, in comparing the treatment results of different lithotriptors was investigated.

Results

We found that the stone-free rate after ESWL for older patients with renal stones, but not for those with ureteric stones, was significantly lower than that of younger patients. Stone parameters measured using NCCT, namely, mean stone density, stone volume, and skin-to-stone distance, were significant predictive factors for successful ESWL for upper ureteric stones. However, caliceal pelvic height, measured by intravenous urography, was a significant predictor of treatment outcomes of lower caliceal stones for only the Piezolith 2300 lithotriptor, and not the other two types of lithotriptors. The additional usage of intravenous analgesic improved the effectiveness quotient and hence treatment outcomes of ESWL. Finally, both logistic regression and matched-pair analysis were found to be feasible approaches for the comparison of the performance of different lithotriptors.

Conclusion

This series of investigations demonstrated how we can apply our knowledge to improve the treatment outcome of ESWL. Based on clinical information, such as age, suitable candidates for ESWL can be identified, and hence better application of ESWL can be achieved. With an understanding of the benefits and limitations of imaging (NCCT and intravenous urography), treatment success can be predicted, and better treatment plans for patients can be formulated. A policy of more liberal use of analgesia during ESWL can also help to improve the treatment outcomes of patients. Finally, with the use of different assessment methods, the true impact of various new technologies or treatment protocols can be assessed, and the results can lead to better understanding of ESWL and also improvement in the treatment outcomes.

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ABBREVIATIONS

AOR	Adjusted odds ratio
CPH	Caliceal pelvic height
EQ	Effectiveness quotient
ESWL	Extracorporeal shock wave lithotripsy
F	Female
LC	Lower Calice
LU	Lower Ureter
LUH	Lower ureteric stone height
M	Male
MC	Mid-calice
MSD	Mean stone density
MU	Mid-ureter
NCCT	Non-contrast computerized tomography
P	Pelvis
ROC curve	Receiver operating characteristic curve
SFR	Stone-free rate
SSD	Skin-to-stone distance
SV	Stone volume
UC	Upper calice
UU	Upper Ureter
VUJ	Vesico-ureteric junction

PRÉCIS OF THE THESIS

Background

Extracorporeal shock wave lithotripsy (ESWL) was first introduced into clinical usage in 1982.[1] With an excellent initial success rate of more than 90%, it has completely revolutionized the treatment of urinary calculi and become the treatment of choice for almost any type of stone in the upper urinary tract. Subsequent development of ESWL includes improvement of the generator design, a better imaging system, and a simplified analgesic regime. These improvements allow greater patient comfort, simplify the user interface, and reduce the capital cost of the system. However, the treatment results of the new lithotriptors have never been as good as those of the first machine, the HM-3 lithotriptor.[2] Therefore, there is a need to improve ESWL treatment strategies to improve the treatment results of our patients.

There are several approaches to improving ESWL treatment outcomes, including better patient selection. Despite the initial enthusiasm for ESWL as a treatment for all urinary calculi, accumulated experience suggests that it does have certain limitations. The current recognized predictors of treatment success include stone size, stone site, and presence of a ureteric stent, among others. With greater understanding of ESWL and the application of new technology, new factors are being identified. Nevertheless, one potential factor that has been overlooked is patient age. In an early report that assessed the prognostic factors for the treatment outcomes of the HM3 for renal stones, patients aged > 60 years had the poorest stone-free rate (SFR) of all age groups.[3] However, there was little discussion of this finding until a recent report that elderly patients had a poorer stone fragmentation rate after ESWL.[4] Therefore, the effect of patient age on ESWL treatment outcomes is an area worthy of further investigation.

Non-contrast computerized tomography (NCCT) has gradually replaced intravenous urography as the first-line diagnostic tool for patients with acute loin pain.[5] In addition to its role in the diagnosis of ureteric stones, NCCT can also provide other useful information, such as stone size (stone volume [SV]), mean stone density (MSD), and skin-to-stone distance (SSD). All of these stone factors may play a role in predicting the outcome of ESWL.

Lower caliceal stones are associated with lower SFRs than stones in other sites in the kidneys. One proposed explanation for this is the anatomical configuration of the lower caliceal collecting system, which hinders the passage of stone fragments.[6] Despite vigorous efforts to identify possible predictive anatomical factors, including infundibular length, caliceal pelvic height, and infundibulopelvic angle, no general consensus has yet been reached regarding the utility of these measurements. This may be due in part to differences in the definition of each factor and inter-observer variation. However, one aspect that has not been properly addressed is the confounding effect of the different lithotriptors used in the various studies, which could limit the generalizability of their results. Therefore, it would be beneficial to assess the effect of different lithotriptors on the applicability of the aforementioned anatomical factors in the prediction of treatment outcomes.

In addition to improvement in patient selection for treatment, modification of treatment protocols may also help to improve the results. In the case of the original HM3 lithotriptor, general anesthesia was almost always necessary. However, for patients treated with the later generations of lithotriptors, less potent analgesics and sedatives are being used. Although the avoidance of general anesthesia is undoubtedly beneficial to patients, there is speculation that less potent analgesics may jeopardize patient outcomes.[7]

Lastly, continuous development in lithotriptor design is essential to further improve ESWL outcomes. However, a standardized comparison method is necessary to assess the efficacy of the new lithotriptors. Although a randomized, controlled trial is the best approach, in real clinical practice, this may not be feasible. Clayman et al. (1989) proposed the use of the effectiveness quotient (EQ), which involves the stratification of treatment outcomes according to stone size and location to control for these two factors.[8] However, the interpretation of this complicated system can be a problem, and the researchers also failed to take other predictive factors into consideration. Therefore, a new approach to the comparison of various new lithotriptor technologies is crucial for the future development of ESWL.

Hypothesis

To improve the treatment outcomes of ESWL, improvements are needed in both the patient selection criteria and ESWL treatment protocol. In addition, better methods for the comparison of the treatment outcomes of different lithotriptors are needed to assess the true impact of the various new technologies. Therefore, the hypotheses tested in this thesis are as follows.

1. Patient age may be a predictor of ESWL treatment outcome.
2. The parameters measured by NCCT may help in predicting treatment outcomes after ESWL for upper ureteric stones.
3. The mixed findings on the applicability of lower caliceal anatomical factors in predicting the treatment outcome of ESWL for lower caliceal stones may be related to the effects of different lithotriptors.
4. Analgesic consumption during ESWL may affect the treatment outcome.
5. The use of different statistical methods or models may help in comparing the treatment outcomes among different lithotriptors.

Objectives

1. To assess the effect of patient age on the SFR after ESWL for urinary calculi.
2. To assess the predictive ability of various parameters measured by NCCT of the SFR after ESWL for upper ureteric stones.
3. To assess the applicability of CPH in the prediction of lower caliceal stone clearance in patients treated with three different lithotriptors within one center.

4. To assess the effect on treatment outcome of the additional usage of intravenous analgesia during ESWL.
5. To demonstrate the feasibility of the use of two different statistical approaches, logistic regression and matched-pair analysis, in comparing the treatment results among different lithotriptors.

Methodology

1. To assess the effect of patient age on the SFR after ESWL for urinary calculi

Patients with solitary radio-opaque urinary stones 5-15 mm in size who received primary ESWL were retrospectively reviewed. Patient and treatment characteristics and treatment outcomes were retrieved. Patients were divided into three age groups for analysis: ≤ 40, 41-60, and > 60 years old. Logistic regression was used to assess the effects of age on the SFR three months after treatment.

2. To assess the predictive ability of various parameters measured by NCCT of the SFR after ESWL for upper ureteric stones

Patients who were suffering from radio-opaque upper ureteric stones, as confirmed by NCCT, and for whom primary in-situ ESWL was planned were prospectively recruited for the study. Patients received ESWL following the standard protocols. The NCCT image was then retrieved by a single radiologist for the measurement of various parameters, including stone size, stone density, and SSD. The primary endpoint of treatment was the SFR after one session of ESWL. Logistic regression was performed to assess the effects of the potential predictors.

3. To assess the applicability of CPH in the prediction of lower caliceal stone clearance in patients treated with three different lithotriptors within one center

Patients with a solitary, radio-opaque, lower caliceal stone 6-10 mm in size who received primary ESWL were retrospectively reviewed. They were treated with one of three lithotriptors, the Wolf Piezolith 2300, Dornier MPL 9000, or Dornier Compact Delta. Pretreatment intravenous urograms were reviewed by a single urologist, and CPH, the vertical distance from the lowermost point of the calyx to the highest point of the lower lip of the pelvis, was measured by another urologist who was blinded to the treatment outcomes of the patients. The primary endpoint was the SFR after three months. The adjusted odds ratios (AORs) of the different potential predictor variables, including CPH, for the overall result and the individual machines, were estimated using logistic regression. The applicability of CPH in the prediction of lower caliceal stone clearance for the different machines was then assessed.

4. To assess the effect on treatment outcome of the additional usage of intravenous analgesia during ESWL

Patients with a solitary urinary stone less than or equal to10 mm in size were retrospectively reviewed. They all received the same analgesic protocol – 50 mg oral diclofenac as a premedication and additional intravenous bolus alfentanil if they experienced discomfort during ESWL. After the analgesic usage was reviewed, patients were divided into two groups, Group A, which received pretreatment oral analgesic alone, and Group B, which received both pretreatment oral analgesia and additional intravenous analgesia during ESWL. The treatment outcomes of the two groups were then compared.

5. To demonstrate the feasibility of the use of two different statistical approaches, logistic regression and matched-pairs analysis, in assessing the treatment results between different lithotriptors

Two statistical approaches, logistic regression and matched-pair analysis, were used to demonstrate the approaches to compare the treatment outcomes of different lithotriptors in different clinical scenarios.

a. Logistic regression

A retrospective review of the treatment outcomes of patients who had received ESWL in a single center between January 1992 and June 2002 was conducted. These patients had been treated with one of three different lithotriptors, the Wolf Piezolith 2300, Dornier MPL 9000, or Dornier Compact Delta. The treatment outcomes were assessed by the SFR three months after one treatment session, retreatment rate, auxiliary procedure rate, and complication rate. Using logistic regression to control for the various factors that may affect treatment outcomes, including lithotriptor type, patient sex and age, history of previous ESWL, stone characteristics (side, site, and size), and the presence of a ureteric stent or nephrostomy tube, the treatment outcomes of the three machines were compared.

b. Matched-pair analysis

After a three-month trial, the treatment results of a new lithotriptor, the Piezolith 3000, were compared with those of an older generation model, the Piezolith 2300. During the trial period, the information of patients treated with the Piezolith 3000 was prospectively collected. Then, patients with solitary, radio-opaque urinary calculi who underwent primary lithotripsy were selected and matched with patients from a database of patients treated between 1992 and 1999 with the Piezolith 2300. Patients were first matched by sex and by the side and site of the stone. For stones other than those in the lower calix or lower ureter, matching was performed by size in terms of the maximum and minimum diameter of the index stone. For lower caliceal and lower ureteric stones, the additional anatomical factors of CPH and the vertical distance of the lower ureteric stone from the pubic symphysis, respectively, were measured. Thereafter, index stones ± 1 mm in size were selected, and the stone with the best matched anatomical factors was chosen. The SFRs at three months for the matched pairs were then compared using McNemar's test.

Results

1. To assess the effect of patient age on the SFR after ESWL for urinary calculi

A total of 2192 adult patients with solitary, radio-opaque urinary stones 5-15 mm in size who had been treated with primary ESWL were identified and divided according to age into three groups: ≤ 40 (579), 41-60 (1026), and > 60 (587) years old. Logistic regression was used to assess the effects of age and other possible predictive factors on the SFR three months after treatment. The results showed that the overall AORs for the SFRs of the 41-60 and > 60 age groups (with the ≤ 40 age group as the reference) were 0.708 (0.573, 0.875) ($p = 0.001$) and 0.643 (0.506, 0.818) ($p < 0.001$), respectively. However, when the patients were divided into renal and ureteric stone subgroups, the SFR of only the former subgroup was affected by age. The AORs for patients with renal stones in the 41-60 and > 60 age groups were 0.665 (95% CI: 0.512, 0.864) ($p = 0.002$) and 0.629 (95% CI: 0.470, 0.841) ($p = 0.002$), respectively. Age had no effect on the SFR of the ureteric stone subgroup. We concluded that the SFR after ESWL among older patients with renal stones was significantly lower, but not among those with ureteric stones.

2. To assess the predictive ability of various parameters measured by NCCT of the SFR after ESWL for upper ureteric stones

Fifty-five patients (35 males and 20 females) with solitary upper ureteric stones were recruited. The overall SFR after one session of ESWL was 52.7%.

Multivariate analysis showed that stone volume (SV), mean stone density (MSD), and skin-to-stone distance (SSD) were significant predictors of treatment outcome. However, because of the effect of stone size on MSD measurement, patients were divided into two groups, SV $\leq$ 0.2 cc and SV > 0.2 cc (based on the scattered plot of the relationship between SV and MSD). For patients with SV $\leq$ 0.2cc (20), the SFR was 85%, and the outcome was independent of all CT parameters. However, for patients with SV > 0.2 cc (35), the SFR was only 34.3%, and multivariate analysis showed that MSD and SSD were significant predictors of the SFR. Among these 35 patients, for those who had either MSD $\leq$ 600 or SSD $\leq$ 85 mm, the SFR was 53.9% (9/17). By combining these algorithms (SV $\leq$ 0.2 cc or MSD $\leq$ 600 or SSD $\leq$ 85 mm), the overall SFR was improved to 70.3% (26/37). We concluded that the measurement of SV, MSD, and SSD by NCCT can help to predict the treatment outcome of ESWL for upper ureteral stones. By formulating algorithms based on these parameters, the SFR after ESWL for upper ureteric stones can be improved.

3. To assess the applicability of CPH in the prediction of lower caliceal stone clearance in patients treated with three different lithotriptors within one center

Four hundred and seventy adult patients with solitary, radio-opaque, lower caliceal stones 6-10 mm in size who received primary ESWL between January 1992 and June 2002 were identified. Their pretreatment intravenous urograms were reviewed and their CPH measured. The primary endpoint was the SFR after three months. The AORs of the different potential predictor variables for the overall result and the individual machines were estimated using logistic regression. In the overall analysis, only stone size and machine type were associated with the SFR. Smaller stones had better clearance, whereas the MPL 9000 appeared to have the best performance, followed by the Piezolith 2300. However, in the subgroup analysis, CPH became a significant predictor of the SFR for the Piezolith 2300 (AOR = 0.960, 95% CI 0.925-0.960; p = 0.031), but not for the other two machines. Therefore, we concluded that CPH was useful only in the prediction of the SFR for lower caliceal stones treated with the Piezolith 2300, but not for those treated with the other two machines. The usefulness of one anatomical factor assessed by the treatment outcome of one lithotriptor should not be extrapolated to other machines.

4. To assess the effect on treatment outcome of the additional usage of intravenous analgesia during ESWL

Five hundred and twenty adults who underwent primary ESWL with the Compact Delta between April 1999 and March 2002 were retrospectively reviewed. Of these, 306 (58.8%) had received only pretreatment oral analgesia prior to ESWL (Group A), and the other 214 (41.2%) had also received intravenous analgesia during the procedure (Group B). Our results showed that there was no difference between the maximal energy levels and mean shock numbers of the two groups. The SFRs after three months for Groups A and B were 38.2% and 44.9%, respectively (p = 0.100). The overall retreatment and auxiliary procedure rates for Group A were 40.8% and 12.7%, respectively. For Group B, the corresponding rates were 35.0% and 18.2%. The additional use of intravenous analgesia improved the EQ by 17.7% (from 0.249 [Group A] to 0.293 [Group B]). We concluded that the additional use of intravenous analgesia during ESWL resulted in improvement in the EQ.

5. To demonstrate the feasibility of the use of two different statistical approaches, logistic regression and matched-pairs analysis, in assessing the treatment results between different lithotriptors

a. Logistic regression

During the study period, 3044 patients with solitary, radio-opaque urinary stones ≤ 15 mm in size (in total, 3123 stones – 1449 treated with the Piezolith 2300, 780 with the MPL 9000, and 894 with the Compact Delta) who had been treated with primary ESWL were identified. Using logistic regression, the AORs of the SFR after three months for the Piezolith 2300 and MPL 9000 (using the Compact Delta as the reference category) were 1.38 (95% CI 1.15-1.65) and 1.72 (95% CI 1.39-2.11), respectively. The patients treated with the MPL 9000 had a significantly lower retreatment rate (AOR = 0.57, 95% CI 0.48-0.69) than had those treated with the other two machines. No significant difference was identified in either the auxiliary procedure or complication rate among the three machines. Therefore, based on the multivariate analysis results, of the three lithotriptors, the MPL 9000 had the best treatment outcome in terms of the SFR and retreatment rate.

b. Matched-pair analysis

During the three-month trial period, 128 patients with solitary, radio-opaque urinary calculi were treated with the Piezolith 3000. They were matched with 1226 patients who had been treated by the same team between January 1992 and March 1999 using the Piezolith 2300. After the matching process, 25 matched pairs were found. McNemar's test revealed no statistical difference between the SFR (36%) for the Piezolith 3000 and that (48%) for the Piezolith 2300. We concluded that there was no significant difference between the outcomes of these two generations of the piezoelectric lithotriptor.

Conclusion and Interpretation

This series of investigations demonstrated how we can apply our knowledge to improve the treatment outcomes of ESWL. Knowing that the results of ESWL in elderly patients with renal stones are not optimal, alternative treatments should be considered, especially when there are other coexisting factors associated with poor treatment outcome. With an understanding of the benefits and limitations of imaging (intravenous urography and NCCT), treatment success can be predicted, and better treatment plans for patients be formulated. A policy of more liberal use of analgesia during ESWL can also help to improve the treatment outcomes of patients. Finally, with the use of different assessment approaches, the true impact of various new technologies or treatment protocols can be assessed and the outcomes of ESWL be improved.

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Section 1

Introduction and Background of Urolithiasis

Chapter 1

History and Epidemiology of Urolithiasis

Urolithiasis is an ancient disease. The oldest stone discovered is a bladder stone found in an Egyptian mummy, dating from around 5000 BC, at El Amrah, Egypt. In the fourth century, Hippocrates described the presence of urinary stones, and in his famous oath said, "I will not cut, even for the stone, but leave such procedures to practitioners of that craft." Although urolithiasis is a very old and common problem, the composition and pathogenesis of urinary stones were not well studied until the sixteenth century. In the twentieth century, there was a dramatic change in the nature of the disease. Previously, because of poor personal hygiene and nutrition, bladder stones were the most common stone type encountered. However, over the past 100 years, with the improvement in the socioeconomic status of the population as a whole and better nutrition and hygiene, the incidence of bladder stone disease has dramatically decreased. [1] Nonetheless, there has been a rapid increase in the incidence of renal and ureteric urolithiasis, especially in the Western world. [2-5] This increased incidence appears to be related to high animal protein intake [6] and the obesity pandemic. [7, 8]

The etiology and management of bladder stones are completely different from those of upper tract (renal and ureteric) stones. The subsequent discussion focuses mainly on the latter.

I Epidemiology

A. Prevalence and incidence worldwide

Urolithiasis affects 5-15% of the population worldwide. As mentioned, upper tract stones are more common in developed countries and less common in countries the economies of which are weaker and tied more to agriculture. The life-long expectancy of stone formation in men closely follows the pattern of increasing gross domestic product in countries across the world. [9] The life-long incidence varies from up to 20% in the Kingdom of Saudi Arabia to less than 5% in China, with that of most European countries and Japan around 10%.[9]

Another important issue related to stone disease is the high recurrence rate, with a relapse rate of 50% in 5-10 years and 75% in 20 years. [10, 11] Once recurrence has occurred, the subsequent relapse risk is raised and the interval between recurrences shortened.[12]

Asia

Socioeconomic development in Asia is diverse. In Japan, the prevalence of upper tract stone disease is reported to be similar to that observed in Western countries, with a lifetime risk of forming a stone of 10%. [13] However, in other Asian countries, where socioeconomic development is in general inferior to that of Western countries, bladder stones are still more common than upper tract stones. With the improvement in socioeconomic conditions throughout Asia, the pattern of stone disease is expected to become similar to that of the Western world. The incidence of upper tract stones in Saudi Arabia, Turkey, and Taiwan is reported to have been increasing since the 1990s. [13]

China and Hong Kong

An epidemiological study of renal calculi in Chinese people revealed that the prevalence rate was 8% and 5% in men and women, respectively. [14] A report on a nationwide postal questionnaire in Taiwan indicated that the overall prevalence was around 9.6%, [15] and the prevalence of having upper tract stone disease was found to be three times greater in males than in females (14.5% and 4.3% respectively). Also, an increased risk of having the disease among those with a family history of stone disease was observed. In a recent telephone public survey carried out in Hong Kong, the calculated household prevalence of urinary calculi was 6.9%. [16]

B. Risk factors for renal stone formation

Conditions predisposing to stone formation are shown in Table 1.1. The presence of risk factors increases the risk of renal stone recurrence. Corrective measures directed towards these risk factors such as diet modification are emerging nowadays and might have a potential role in reducing recurrence. [17] Some of these risk factors are discussed in the following section.

Sex and age

Men have traditionally had a higher incidence of stone formation than have had women, with a male-to-female incidence ratio of 2:1.[5] This is probably related to both genetic and socioeconomic factors. Male patients in general have a higher animal protein intake and engage in more outdoor and/or manual work, which leaves them relatively dehydrated because of profuse sweating. However, it has been observed that the gender gap is becoming less significant in the United States. [5] The majority of patients experience their first stone at around 25-50 years of age, which is the most active and productive stage in their career. Therefore, the socioeconomic impact of the disease could be very significant.

Familial factors

People with a family history of stone disease have a 2.5 times higher risk of having stone disease than has the general population. [18] This is probably multifactorial, and includes dietary, environmental, and genetic factors.[19] Some diseases, such as cystinuria and primary hyperoxaluria, are inherited diseases that predispose to stone formation. Similar living and dietary habits may account for the increased risk of stone formation within the same family.

Dietary factors

The chemical constituents of stones and their concentration can be affected significantly by dietary factors; therefore, dietary modification is one of the keys to the prevention of stone recurrence. Dietary factors that can affect stone formation include fluid intake, calcium, animal protein, and caloric intake, calcium oxalate and related constituents, sodium, potassium, and so forth. Some of the more important factors are discussed.

Among all dietary factors, fluid intake is the probably the most important. Several studies, both observational and randomized, have demonstrated the positive effects of increased fluid intake in preventing stone formation.[6, 18, 20, 21] Therefore, patients at risk for stone formation should drink enough fluid to produce a daily urine output of at least two liters.

The traditional belief that decreased calcium intake will help to decrease the risk of stone formation has been disproved by several prospective studies. [6, 18, 20] The underlying mechanism is probably related to the increase in unbounded free oxalate inside the intestinal lumen due to the decrease in calcium intake, which in turn leads to an increase in oxalate absorption and hence an increase in the urine oxalate level and risk of stone formation.[22] Therefore, the current advice is to maintain an adequate daily calcium intake of about 800-1000 mg per day.

High animal protein intake increases the risk of stone formation. The excessive intake of such protein increases calcium and uric acid excretion and lowers the urine pH. (i.e., the urine becomes more acidic)[23] Also, patients with high animal protein intake usually have a higher body mass index (BMI), which has been shown to be another risk factor for stone formation, independent of dietary factors.[8]

Urinary oxalate is an important factor in stone formation. There are several sources of urinary oxalate. The majority of dietary oxalate after absorption is excreted unchanged in urine. However, the absorption of dietary oxalate varies, ranging from 10 to 50%,[24] and is affected by many factors, including cooking method,[25] dietary calcium level,[23] and the presence of *Oxalobacter formigenes*.[24,25] Urinary oxalate is also derived from endogenous production, including the metabolism of glycine, glucolate, and vitamin C. However, the usual daily intake of vitamin C does not increase the risk of stone formation.[20,26]

High sodium intake is also found to be a risk factor for stone formation because of its effects on the level of urinary calcium.[27,28]

Hot climate

Studies suggest that people who work in a hot climate have a higher risk of stone formation.[29] Besides the possibility of dehydration, due to increased sweating and less availability of drinking water, related to such a climate, it is also suggested that increased exposure to sunshine increases vitamin D production in the skin, which leads to an increase in the level of urinary calcium. [30]

Another report suggests that the increase in global temperatures (global warming) could lead to an increase in kidney stones and again, dehydration is probably the link between the warmer climate and stone formation. [31]

Occupational factors

People who work in a hot environment, such as those in the steel industry [32] or those who do outdoor work, have an increased risk of stone formation, which is probably related to their increased sweating and decreased urine volume.

Associated diseases

Many diseases can increase the risk of stone formation, including (1) diseases that directly affect urine chemical composition, such as hypercalcemia due to hyperparathyroidism, hyperuricemia/gout, and renal tubular acidosis; (2) diseases that result in urine stasis, such as congenital structural abnormalities including ureteropelvic junction obstruction, caliceal diverticulum, or a horseshoe kidney; (3) diseases that predispose to urinary tract infections, such as a neurogenic bladder, vesicoureteric reflux, and so forth, and (4) other conditions the underlying mechanisms of which are still unclear, including obesity [8] and diabetes mellitus. [33]

II Pathogenesis of Urolithiasis

Renal stone formation is a multifactorial process that is characterized by various environmental and metabolic abnormalities. The process includes at least two parts – the physical chemistry related to crystal formation and crystal retention and aggregation that can result in stone formation. A detailed discussion of these mechanisms is beyond the scope of this review; hence, a brief overview of the basic mechanism is given as follows.

Crystal formation

The key physical chemical process in stone formation is the supersaturation of certain crystallizable ions in urine, which leads to crystal formation. When the concentration of two crystallizable ions increases and the *concentration product* (the result of multiplying the concentrations of the two ions) goes above a certain level, (the *solubility product*) crystal growth, or heterogeneous nucleation, starts. If the concentration product increases further, then (the *formation product*) spontaneous crystal formation will occur. Besides changes in the concentration of particular ions, other factors that can affect the chance of crystal formation include solvent amount (urine volume) and urinary pH. The situations of commonly encountered stones, including calcium-related (calcium oxalate and calcium phosphate), uric acid, struvite, and cystine stones, are discussed below.

Calcium-related stones are the most commonly encountered stones (around 80-85%), and include calcium oxalate and calcium phosphate stones. Metabolic abnormalities include hypercalciuria, hyperoxaluria, and hyperphosphaturia. Hyperuricosuria can facilitate calcium stone formation by providing a crystal nidus for crystal growth (heterogeneous nucleation). There are also inhibitors of crystal formation. For example, citrate and magnesium are important stone inhibitors, and a decrease in the urinary excretion level of either of these is linked to an increase in stone formation.

Magnesium-ammonium-phosphate stones, known as struvite stones, are more common in women. They are almost always associated with urinary tract infections caused by urease-producing bacteria such as *Proteus mirabilis*. The splitting of urea results in increases in levels of urinary ammonia, bicarbonate, carbonate, and pH. These chemical changes lead to urinary supersaturation of struvite, which results in crystal formation. [34]

Uric acid stones are less common and are usually radiolucent. Risk factors that predispose to uric acid stone formation include hyperuricosuria, low urinary volume, and persistently low urinary pH. The hyperuricosuric state of patients with chronic diarrhea, myeloproliferative disorders, or diabetes mellitus explains their susceptibility to this type of stone formation. [35]

Cystine stones are rare. They are associated with cystinuria, a rare autosomal recessive hereditary disorder, which causes a 10-fold increase in urine cystine excretion because of a defect in the intestinal and renal tubule transport of cystine. [36]

Crystal retention, aggregation, and growth

In addition to the formation of crystals secondary to supersaturation, mechanisms are required for the retaining of crystals and their further aggregation and growth to stones. Several theories have been proposed to explain the steps of stone formation; however, none of them seems to be complete, and this has raised the suspicion that the mechanisms underlying the formation of different stones (different phenotypes) may be different. [37] These theories include crystal-induced renal injury, [38, 39] intersititial theory (Randall's plaque formation), [40, 41] tubular theory, [42, 43] urinary stasis due to anatomical problems, [37] among others.

III Conclusion

Upper urinary stones are more common in affluent countries and less common in countries the economies of which are weaker and tied more to agriculture. Because of rapid economic development, possible global warming effects, the increase in animal protein and lipid consumption, and the diabetes pandemic, the prevalence of urolithiasis is expected to increase in Hong Kong and mainland China. As the majority of patients are males aged 30-60 years, the associated loss in socioeconomic productivity is another concern. Therefore, further improvement in the management of urolithiasis is important for both health care and the economy. A better understanding of the disease, which will result in better management protocols, will definitely benefit both patients and society.

Table 1.1 Common risk factors for stone formation

Personal factors
- Male sex
- Family history
- Previous stone events

Acquired factors
- Dietary factors
    - Insufficient fluid intake
    - Excessive animal protein and salt intake
    - Excess caloric intake, high chocolate consumption
    - Insufficient intake of fruit and potassium-rich vegetables
- Environmental factors
    - Hot climate
    - Occupation related to a hot environment

Associated diseases
- Hypercalcemia
    - Primary hyperparathyroidism
    - Malignancy
    - Immobilization
- Hypercalciuria
- Gout and Hyperuricosuria
- Hyperoxaluria
- Hypocitraturia
- Congenital abnormality of the urinary tract
    - Ureteropelvic junction obstruction
    - Horseshoe kidney
    - Medullary spongy kidney
    - Caliceal diverticulum
- Renal tubular acidosis (type I)
- Recurrent urinary tract infections
- Obesity
- Diabetes mellitus

Medications
- Loop diuretics
- Antacids
- Indinavir
- Corticosteroids

Chapter 2

Overview of the Management of Urolithiasis

Patients with renal stones commonly present with pain, hematuria, infection, and other symptoms. However, renal stones are increasingly being found incidentally in association with the increase in the utilization of imaging investigations, such as those undertaken during routine health checks. In this chapter, common presentations of renal stones are discussed, and an overview of the management of stone disease is given.

I Clinical Presentation

Pain

Pain is the most common presentation of ureteric stones. Typical ureteric colic is due to an obstruction caused by the stone, which stimulates an increase in peristalsis of the proximal ureter, resulting in colicky pain. The pain also typically radiates down to the groin and genital region. The subsequent increase in pressure also causes distension of the proximal ureter and kidney, which gives rise to dull loin pain. This pain is usually accompanied by nausea and vomiting. There may be associated fever and hematuria. A nonobstructing renal stone may also present with pain, which is usually less severe than that associated with ureteric colic and is localized in the loin region.

Hematuria

Hematuria is present in up to 90% of stone patients, although the majority present with microscopic hematuria. However, in 7-18% of patients experiencing an acute attack of ureteric colic, microscopic hematuria may not be detected during the initial investigation. [44] Therefore, lack of hematuria does not exclude the possibility of urinary calculi.

Infection

Infection can be the cause and/or consequence of stone disease. Typically, infection with a urea-splitting organism, such as *Proteus*, results in alkalization of the urine, which leads to the formation of struvite stones. However, any obstructing stone can lead to secondary infection in the proximal urinary system. Patients may present with loin pain, fever, and chills. In severe cases, patients may present with septicemia or septic shock, two of the few urological emergencies related to stone disease.

Renal impairment

Stones are sometimes found during a workup for impaired renal function. The stone can be either a chronic obstructing ureteric stone or a large renal stone, either of which results in low-grade infection and progressive renal damage.

II Management Overview

The management of urolithiasis can be divided into three phases.

- *Initial assessment and urgent management*

  Formulating the diagnosis and controlling the presenting symptom(s)

- *Definitive management*

  Formulating a definitive treatment plan for the stone

- *Metabolic workup and preventive measures*

  Formulating a treatment plan to prevent stone recurrence

Initial assessment and urgent management

Initial evaluation of the patient with urolithiasis should include a complete medical history and physical examination. Comorbid diseases should be identified, especially any systemic illnesses that may increase the risk of kidney stone formation or influence the clinical course of the disease. (Table 2.1) Other important features are a personal or family history of kidney stones, previous treatments and stone analysis, and any anatomical abnormalities or surgery of the urinary tract. (Table 2.1) A complete medication history can also help to identify those that are known to have increased risk of kidney stone formation. (Table 2.1)

The physical examination should include the assessment of vital signs because fever may be an indication for urgent intervention. This examination often reveals costovertebral angle or lower abdominal tenderness. Urinalysis should be performed in all patients. In the acute setting, laboratory evaluation includes a complete blood count, serum electrolytes, and measurement of renal function, which should also be done as the baseline assessment.

The imaging examination is the most important investigation for establishing the diagnosis. Various imaging modalities can be used for patient assessment, including simple plain radiography, ultrasound examination, intravenous urography, and non-contrast computerized tomography. Non-contrast computerized tomography has become the first line of investigation for ureteric colic, with high sensitivity and specificity for diagnosis. [45]

For ureteric colic, adequate pain control is essential. Nonsteroidal anti-inflammatory drugs have been shown to be better than opioid analgesics in terms of pain control and side effects. [46] However, certain conditions necessitate urgent drainage of the obstructed system. These conditions include pyonephrosis, obstruction of a solitary kidney or transplant kidney, bilateral ureteric obstruction, acute renal failure, or intractable pain or vomiting, among others. Percutaneous nephrostomy and ureteric stenting are both effective for the drainage of the obstructed kidney. Once the acute condition has been managed, a definitive management plan of the stone can be formulated.

Definitive management

There are various options to deal with the stone, including the following.

- Conservative management
- Medical expulsive therapy
- Medical dissolution therapy
- Extracorporeal shock wave lithotripsy
- Ureteroscopy
- Percutaneous nephrolithotomy
- Laparoscopic ureterolithotomy
- Open surgery (including nephrectomy)

Because each treatment has advantages and limitations, when formulating the definitive treatment plan for a patient, factors that may affect the treatment outcome of individual patients need to be considered. These factors can be divided into stone, patient, and surgeon factors. (Table 2.2) After consideration of these factors, the best suitable treatment can be offered to the patient. The details of individual treatment modalities are discussed in the next section.

Metabolic workup and preventive measures

As mentioned, the recurrence rate of urinary stones is high, with 50% of patients having a recurrence in 5-10 years and 75% in 20 years. [10, 11] Therefore, preventive measures are important to minimize the chance of recurrence. Although a comprehensive metabolic evaluation may not be cost effective in all patients who first present with stones, [47, 48] patients with recurrent stone formation should be further evaluated. All stone patients should have their serum calcium level checked to exclude hypercalcemia, and all stone fragments passed should be sent for chemical analysis, if feasible. For those patients diagnosed with uric acid or struvite stones, specific measures should be taken to minimize stone recurrence. (Table 2.3) For first-time stone formers who are found to have calcium-related stones, general lifestyle and dietary advice should be given. This advice should include increasing fluid intake to maintain a urine output of at least two liters per day, decreasing animal protein intake to less than 12 ounces a day, and restricting both dietary sodium and oxalate intake. [21, 49] Restriction of calcium intake is not recommended as this may paradoxically increase risk of stone recurrence because of the increase in gastrointestinal oxalate absorption and hence increase in urinary oxalate level. [50] For recurrent stone formers, the evaluation should include chemical analysis of the stones and 24-hour urine collection for the assessment of urine volume and levels of sodium, calcium, oxalate, magnesium, phosphate, uric acid, and citrate in the urine. The medical management of recurrent or high-risk stone formers should be individualized according to the investigation results.

III Surgical Options for Definitive Stone Management

A brief introduction to common surgical treatments is given in this section.

Open surgery

In the past two decades, there have been significant technical advances in stone management, such that open surgery is now rarely necessary. The traditional open approaches for renal stone removal include anatrophic nephrolithotomy, radial nephrotomy, and pyelolithotomy. The choice of surgery depends on the stone location and load. For stones in the renal pelvis, pyelolithotomy is ideal. However, for a large branched stone, anatrophic nephrolithotomy may be needed to clear the main bulk of the stone. The procedure, first described by Smith and Boyce in 1968, includes complete mobilization of the kidney through a loin incision. The renal pedicle is then clamped. Surface cooling of the kidney by ice is done to achieve hypothermia. An incision is then made over Brodel's line to minimize blood loss, and the caliceal system is entered for removal of the stone. After the stone is cleared, the caliceal system and renal parenchyma are repaired. Finally, the renal pedicle is unclamped. This approach results in some degree of irreversible kidney damage. If the function of the kidney containing the stone is poor (less than 10-15% differential function), then simple nephrectomy might be a better alternative treatment than lengthy endoscopic or open procedures.

For ureteric stones, traditional ureterolithotomy has largely been replaced by endoscopic treatment, using either the ureteroscopic or percutaneous approach. For unusual cases of large ureteric stones (more than 1.5 cm in size), laparoscopic ureterolithotomy is a feasible alternative that can provide nearly 100% stone clearance in one procedure. [51]

Percutaneous nephrolithotomy

Percutaneous nephrolithotomy was first reported in 1976. [52] The procedure involves creating a direct access tract, through the body and usually from the back, into the renal collecting system through which endoscopic stone fragmentation and clearance can be performed. (Figure 2.1) In a standard nephroscope, there is a working channel for the introduction of intracorporeal lithotripsy devices, such as ultrasonic or pneumatic lithtotriptors, for stone fragmentation. Stone fragments are then removed through the nephrostomy tract. Although percutaneous nephrolithotomy is thought to be more invasive than other endoscopic treatment, meta-analysis has demonstrated its safety and efficacy, especially when stones are large, multiple, or complex. [53]

Ureteroscopy

Ureteroscopy involves retrograde visualization of the renal collecting system using a rigid, semi-rigid, or flexible endoscope. The development of modern ureteroscopy began in 1978, when Lyon used a pediatric cystoscope to examine the lower ureter of five adult patients. [54] Subsequently, a specially designed ureteroscope became available. However, its application was mainly for the management of lower and mid-ureteric stones because of the large size of the ureteroscope and lack of a suitable intracorporeal lithotripsy device. With further improvements in fiber optics, deflectability, reduced instrument size, and the introduction of Holmium laser lithotripsy, the role of ureteroscopy in the treatment of upper urinary tract stones has greatly expanded. Currently, even renal stones can be managed by flexible ureteroscopy, with good results. [55]

Extracorporeal shock wave lithotripsy

The introduction of extracorporeal shock wave lithotripsy (ESWL) in the early 1980s revolutionized the treatment of urolithiasis and provided an apparently near-ideal minimally invasive procedure. Shock waves that are generated by a source external to the patient propagate through the body before being focused on a kidney stone. These waves cause stone fragmentation directly by producing mechanical stress or indirectly by collapsing the cavitation bubbles. The initial result of ESWL was promising, with a greater than 90% success rate achieved in dogs and human. [56] Although the subsequent development of ESWL has been less satisfactory, it remains the most commonly performed procedure to treat stone disease. A more detailed discussion of its principles and development is provided in the next chapter.

IV Conclusion

In the past two decades, there have been significant technical advances in urinary stone management, such that open surgery is now rarely necessary. The development of ESWL and the refinement of endoscopic technology and techniques allow urologists to manage stones in any part of the urinary tract with minimal complications. Familiarity with individual techniques and their advantages and limitations is crucial for formulating definitive treatment plans for individual patients.

Table 2.1 Important factors to identify during history taking

Presence of systemic illness

- Endocrine disease
  - Primary parathyroidism
  - Gout
  - Diabetes mellitus
- Gastrointestinal disease
  - Inflammatory bowel disease
  - History of enteric surgery or bypass surgery

Known kidney disease

- Past history of stone disease
- Renal insufficiency
- Anatomical abnormality
  - Horseshoe kidney
  - Ureteropelvic junction obstruction
  - Solitary kidney
  - Urinary diversion
  - Previous renal or ureteric surgery

Drugs that are related to stone formation

- Carbonic anhydrase inhibitors (e.g., topirimate)
- Calcium supplement with vitamin D
- Indinavir or sulfadiazine
- Ephedrine
- Triamterene

Table 2.2 Factors for consideration in planning definitive stone management

Stone factors

Stone site

Stone size

Stone composition

Kidney function and associated abnormalities

Patient factors

General medical condition

Body build

Social status

Surgeon/Institutional factors

Availability of facilities or expertise

Table 2.3 Specific measures for the prevention of uric acid, struvite, and cystine stone recurrence

Uric acid stones

Low purine diet

High fluid intake

Alkalization of urine

Struvite stones

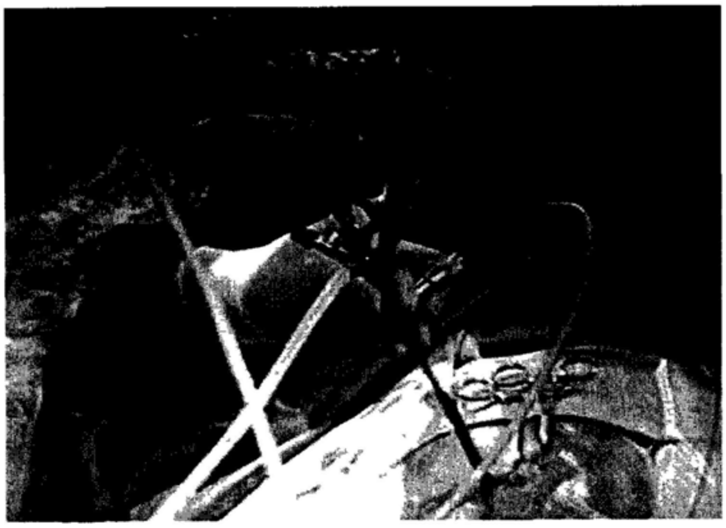
Prevention of recurrent urinary tract infections and treatment of possible underlying causes

Cystine stones

High fluid intake

Chelating agents

Figure 2.1 Percutaneous nephrolithotomy.



Section 2

Discovery and Development of Shock Waves in Medicine

Chapter 3

Development and Application of Shock Waves in Medicine

I History of the Discovery of Shock Waves

Shock waves are high-energy pressure amplitudes generated in fluid media, such as air or water, by an abrupt release of energy within a small space. The waves propagate according to physical laws of acoustics, and are transmitted through media with low attenuation. The interest in shock waves started from a military program. In the 1950s, Dornier, a German aerospace firm, took note of the different degrees of injuries sustained by crew members inside a tank turret after the tank was hit by a shell. This phenomenon was attributed to the relationship of each crew member's position as it related to the entry point and distribution of shock waves throughout the tank turret. An unusual pattern of metal fatigue in aircraft was also observed and thought to be caused by the previously unrecognized effects of shock waves. It was postulated that shock waves produced by supersonic aircraft were being focused inadvertently by contours of one part of the plane's fuselage onto another part of the plane, which resulted in the acceleration of metal fatigue. To explore these propositions, Dornier established a program to develop a system for the production of reproducible focused shock waves. In subsequent investigations, an engineer noted the effect on biological tissue (pain as from an electrical shock) when in contact with the shock wave set up. This phenomenon led to further investigation of the effect on biological structures. Thereafter, the idea of using focused shock waves to fragment human kidney stones arose, and a grant from the German government was obtained.

In the early 1970s, an experimental program was set up in Munich, lead by Chaussy and colleagues. After 10 years of continuous efforts in in vitro and animal research, the first human trial of shock wave therapy on a renal stone was performed in February 1980. [56] The success of this human trial opened up a new chapter in minimally invasive surgery for urolithiasis, the details of which are discussed in Chapter 4.

II Mechanism of Shock-Wave Action

There are several mechanisms by which shock waves fragment a stone. One is the tensile and shear stress acting on the stone due to the propagation of shock waves into the stone. This effect occurs when a pressure wave enters the anterior surface of the stone. The tensile stress between the transmitted wave in the stone and the reflected wave, together with the shear stress created, results in stone breakage. Similarly, when the shock wave leaves the stone, tensile stress is created at the exit site and results in stone fragmentation at the posterior surface of the stone (the spalling effect). [57] This is the first mechanism that was proposed for stone fragmentation by shock waves. (Figure 3.1a)

However, observation of the attenuation of the fragmentation effect of shock waves by even minimal static excess pressure in an exposure vial and the failure of stone fragmentation in viscous media led to the discovery of another important mechanism of stone fragmentation – the cavitational effect. [58, 59] High-speed photographs show the formation of series of bubbles after a wave propagates through a stone. [60] The negative pressure in the trailing part of the pressure pulse causes bubbles to grow at the nucleation site, which is an inhomogeneity in the fluid. During the negative pressure wave, the pressure inside the bubble falls below the vapor pressure of the fluid, which results in the formation of vapor and growth of the bubbles. (Figure 3.1b) The bubbles are not stable and collapse in a few milliseconds. Their collapse results in microjets, which can slowly erode the surface of the stone. (Figure 3.1c) [61] This cavitational effect is believed to be one of the main mechanisms of stone fragmentation.

It was observed that the first cleavage plane in a stone is either parallel or perpendicular to the wave propagation, which cannot be explained by the above two mechanisms. Therefore, a third mechanism, "squeezing," was suggested by Eisenmenger, [57] whereby the positive part of the pressure wave acts on the stone by quasistatic squeezing, which induces cleavage of the stone either parallel or perpendicular to the wave propagation. (Figure 3.1d)

Finally, the mechanical effect of shock waves on a stone results in the formation of microcracks. The accumulated effects of the waves lead to the propagation and coalescence of these microcracks and hence stone fragmentation. This mechanism of stone fragmentation is related to the dynamic fatigue of the stone under the stress of the repeated application of shock waves.

In summary, all of these mechanisms contribute to the process of stone fragmentation by ESWL. Some of them, especially cavitational effects, may also be related to other clinical applications and to potential complications of shock wave application in medicine.

III Current Applications of Shock Waves in Medicine

In addition to being one of the first-line treatments for urolithiasis for the past two decades, shock waves have been used in other branches of medicine. Other stones that can be fragmented by shock waves include bile duct stones [62, 63] and pancreatic and salivary gland stones. [64] Shock wave therapy for gallstones is not effective, however, because of their tendency to multiply and their frequent recurrence secondary to underlying gall bladder dysfunction. [63]

Shock waves are also used for treatment of other urological conditions, including Peyronie's disease [65, 66] and chronic pelvic pain syndrome. [67]

Lastly, shock wave therapy is frequently employed by orthopedic surgeons in the management of conditions such as tendinosis calcarea, epicondylitis humeri radialis, plantar fasciitis, delayed bone healing, and nonunion of long bones. [68-70]

IV Conclusion

The introduction of shock wave therapy in medicine has opened up a new horizon of treatment for various medical conditions. The use of an extracorporeal energy source and the direct transmission of energy through the body had provided a minimally invasive approach for patient treatment, and the technology has been applied to several medical problems, including renal stones, salivary gland stones, and various orthopedic conditions. However, extracorporeal shock wave lithotripsy for renal stones remains the most influential clinical application of shock wave energy and has completely revolutionized the approach to renal stone disease. The nature and principles of extracorporeal shock wave lithotripsy are discussed in the next chapter.

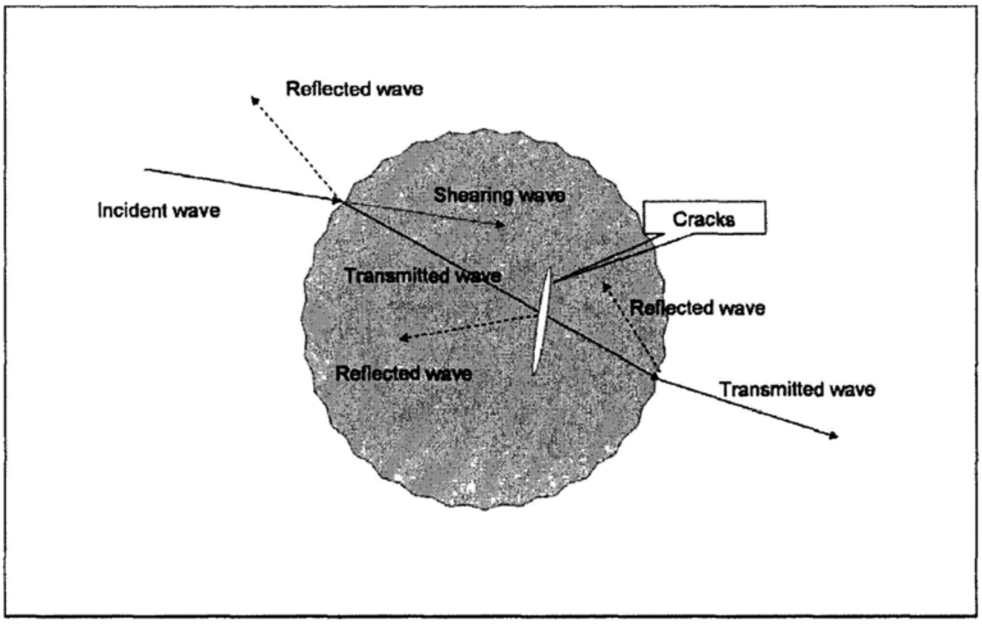
Figure 3.1 The mechanism of stone fragmentation by shock wave:

a) Tensile and shear stress;

b) and c) Cavitation; and

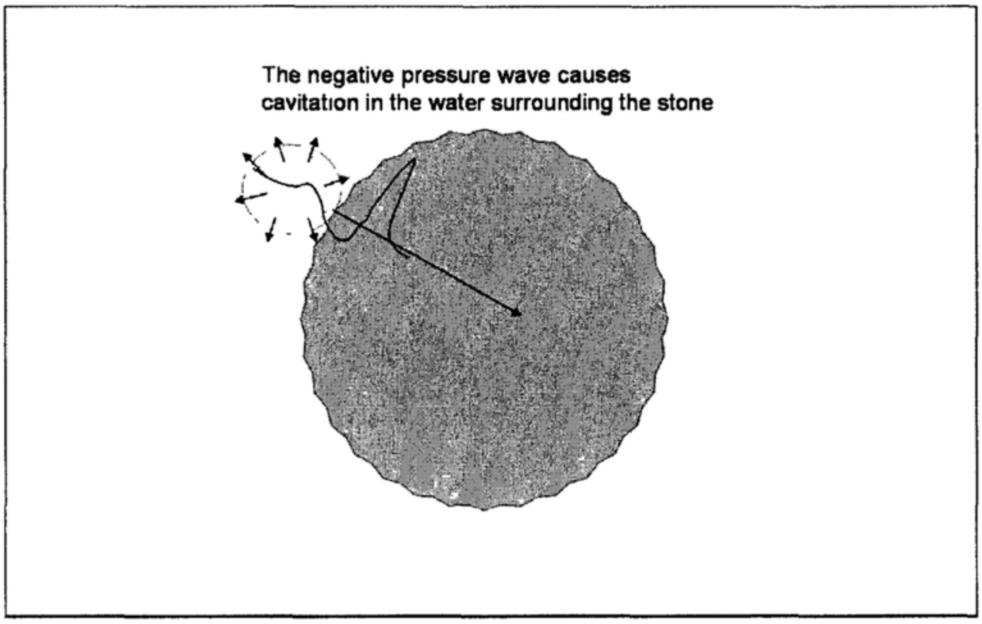
d) Quasistatic squeezing.

a. **Tensile and shear stress**

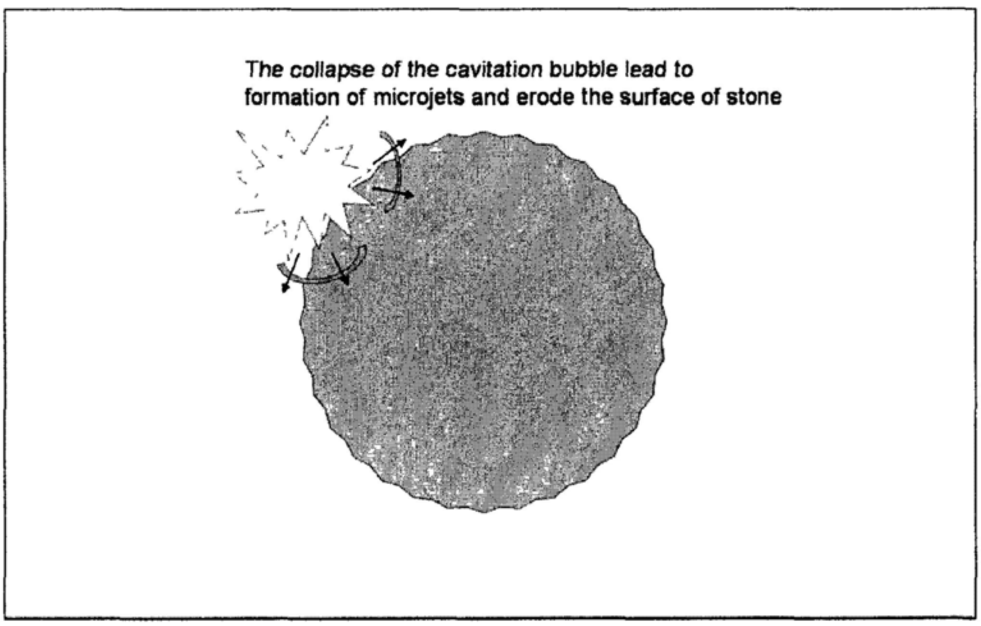


b and c. **Cavitation**

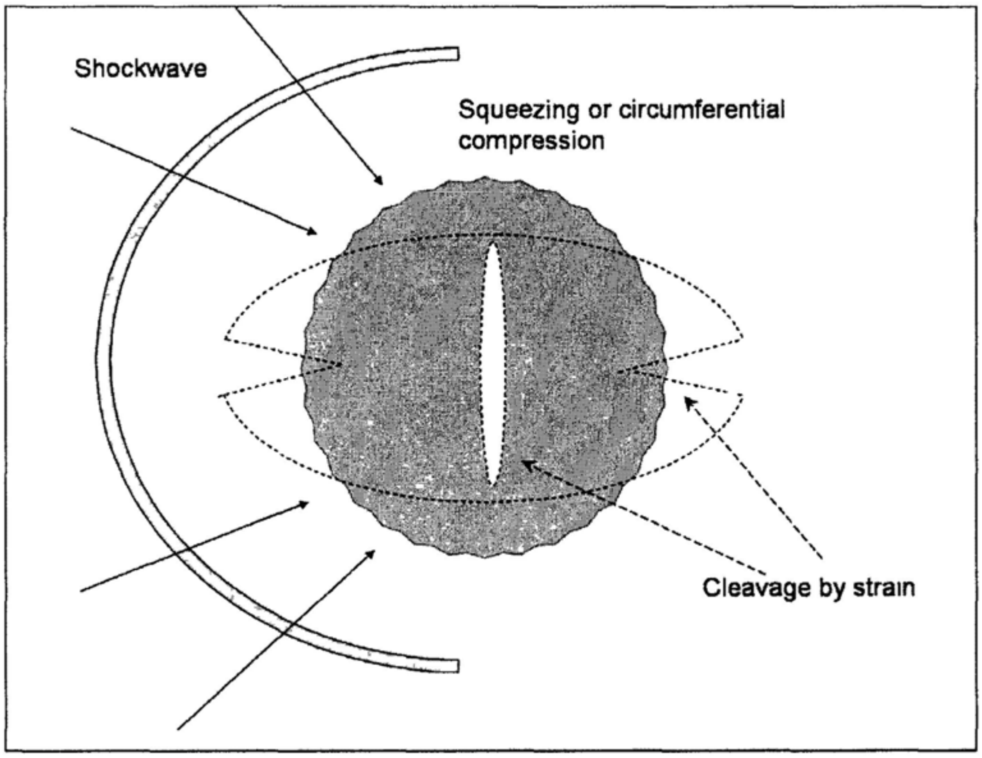
(b)



(c)



d. **Quasistatic squeezing**



Chapter 4
Development of Shock Wave Lithotripsy for the Treatment of Urolithiasis

Shock wave therapy is used in many branches of medicine, but its most common application in modern medicine is extracorporeal shock wave lithotripsy (EWSL) for the treatment of urolithiasis. Although ESWL has been used for more than 25 years, the technology and techniques are still evolving. A brief summary of the history of the development of ESWL and its current status in urology follows.

I Early Experimental and Clinical Research

Following the establishment of the experimental program in Munich, a series of studies was performed. These investigations showed that focused shock waves could be reproduced in a laboratory environment with controllable outputs and effects. It was found that the energy of shock waves could be transmitted through biological tissue without significant side effects. Most importantly, the focused shock waves, after being transmitted through tissue, remained sufficiently strong for stone fragmentation.

In the late 1970s, animal studies were performed with human renal stones implanted into the kidneys of dogs. After radiographic localization, focused shock waves were then applied to the stones. Of the sixty dogs surgically implanted with renal pelvic stones, 96% were treated successfully. [56] These experiments demonstrated not only that stones inside the body could be fragmented by an extracorporeal shock wave system but also that the resulting stone fragments could pass out of the body readily. The success of these experiments led to exploration of the use of the system in humans.

Early clinical studies

A lithotriptor prototype (Human Machine-1[HM-1]) was developed by Dornier. The first human trial was performed in February 1980. [56] The patient was a man who suffered from a right renal stone. The stone was broken into spontaneously dischargeable fragments, and follow-up showed that all of the stone fragments passed spontaneously. Following the success of this trial, more and more cases were treated by ESWL and all showed encouraging results. Modification of the HM-1 led to the development of the HM-2, with simpler operations and electrode changes. The system was still mainly used for the treatment of small, nonobstructive renal pelvic stones, and produced SFRs of up to 90%. [71]

In 1984, the first commercial model, the HM-3 lithotriptor, was introduced by Dornier. Because of the excellent results provided by Dornier and German urologists, approval of general marketing of the HM-3 was promptly granted by the Food and Drug Administration (FDA) of the United States. This ushered in the era of ESWL for the management of urinary calculi.

II The Development of Modern Shock Wave Lithotriptors

The remarkable success of the Dornier HM-3 lithotriptor quickly attracted the attention of other investigators, resulting in the rapid evolution of various modifications of both the technology and techniques of shock wave lithotripsy. All of the modifications were aimed at overcoming the limitations of the HM-3 to improve the results. The modifications in lithotriptor design can be classified according to the different parts of a lithotriptor, that is, the generator and focusing system, coupling mechanism, and imaging system.

Shock wave generator and focusing system

The first shock wave generator was electrohydraulic. [56] Several other generator systems, including electromagnetic, [72] piezoelectric, [73] and microexplosive[74] systems were subsequently developed. Except for the microexplosive system, these generator systems are still in clinical use.

In the HM-3, electrohydraulic technology was used for the generation of shock waves, and involved a spark gap within a fluid medium. During each discharge of electricity, a spark would form between two electrodes, producing a shock wave. Divergent shock waves were then focused by an ellipsoid reflecting surface onto a targeted zone (the second focus of the ellipsoid surface). Although the electrohydraulic system is the first system that was developed, it is regarded to provide the least consistent energy source [75] because of the variability in the current pathway between the tips of the two electrodes. The wearing of the electrode tips by sparks also resulted in the widening of the gap between the two tips, which further affected the consistency of the shock waves. Therefore, the focal zone of the HM-3 and other electrohydraulic lithotriptors was relatively large. Also, the wear and tear on the electrodes required their frequent replacement to maintain the quality of the shock waves. Because of these problems, different shock wave generating systems were developed. The two systems that are commonly used today are electromagnetic and piezoelectric generators. Because of the geometry of each system and the shock waves produced, a specific focusing system for shock waves is necessary for each system.

Electromagnetic generators have a membrane (either planar or cylindrical) [72, 76] that vibrates during the change of the magnetic field and produces a series of shock waves. A convex acoustic lens is used to focus planar waves on the target, whereas a parabolic reflecting surface around a cylindrical generator is used for the focusing of cylindrical waves. The main advantage of the electromagnetic system is the durability of the membrane, which can be used for consistent shock wave production; each membrane can produce several hundred thousands of shocks. In addition, the energy level of the electromagnetic generator can be finely adjusted with good reproducibility, and the system can produce a small precise focal zone with high peak pressure changes. This is now the most commonly used generator design in modern lithotriptors.

Piezoelectric generators have a spherical array of piezoelectric crystals. [73] The application of an electric charge leads to the expansion and then collapse of the crystals, which produces shock waves. The spherical arrangement of the crystals produces shock waves that are directly focused into the center of the sphere, which results in a very tight focal point with high peak pressure. The other advantage of the system is that with the relatively wide angle of shock wave entry, the pain that occurs at the skin level is much less than that of the other systems. However, this type of generator is not as popular as the other two types, especially in the United States, [77] which could be related to its small focal zone and reduced power, compared with the other two sources.

Coupling mechanism

The water bath employed by the HM-3 served as a very effective coupling medium for the transmission of shock waves into the patient's body. However, the large size of the machine, the inconvenience to physicians and patients, and the potential problems in frail patients with compromised cardiopulmonary function led to the exploration of other means of coupling. A semi-water bath/water basin was devised but was still not very convenient. A water cushion with membranes of acoustic density similar to that of the skin was subsequently developed and has become the mainstream coupling system in dry head lithotripsy.

Imaging system

During ESWL, the targeted stone must first be located; then, the focal zone of the generator is positioned over the stone. Because of the initial use of a water bath in the HM-3, a radiographic system was used for the localization of the stone. However, with the development of dry head lithotriptors and the consideration of radiation exposure during localization and the monitoring of treatment progress, an ultrasound system has been incorporated in most modern lithotriptor systems.

Treatment protocol

In addition to design modifications of the machine, there have been numerous changes in the treatment protocol of ESWL. In the original HM-3 system, patients with all types of stones were usually treated under general anesthesia, with the shock wave delivery rate synchronized with the patient's heart rate. However, with increasing experience in ESWL, modifications of the pain control protocol and shock wave delivery rate have been introduced.

Patient selection

Despite the initial success of ESWL in managing all types of urinary stones, there is increasing recognition of its limitations in comparing it to other treatment options. Therefore, general guidelines based on stone characteristics are available to facilitate treatment planning. For example, ESWL is more suitable for treatment of renal stones less than 2 cm in size, whereas percutaneous nephrolithotomy may provide better clearance of stones greater than 2 cm. [78, 79] Stone site also affects the treatment outcome; for example, the results of ESWL for lower pole stones are notoriously poor. [80] Hence, alternatives may need to be considered, especially where and when the stone is associated with other unfavorable factors, such as size. [81]

Another important factor that may affect ESWL outcome is stone composition. Cystine stones, for example, are known to be resistant to shock wave energy. [36]

Pain control protocol

One of the main changes in ESWL protocol is pain management during treatment. With the original HM-3 lithotriptor, general anesthesia was almost always necessary because of the high power of the machine. However, less potent analgesics and sedatives are being used among patients treated by the newer generation of lithotriptors, in part because of the modification of the generator design to create a wider aperture at the shock wave source. This modification decreases the energy density at the skin entry point and results in less pain. It also decreases the total energy output of some machines, which helps to decrease the analgesic demand. [82] Therefore, the majority of patients are now treated with simple analgesics and sedatives. Also, as the procedure can be done as a day-case procedure, there is a more rapid turnover of patients.

Shock wave delivery rate

In the initial clinical trial of the HM-1, it was observed that an uncoordinated release of shock waves resulted in cardiac arrhythmias. Therefore, in the HM-3, shock waves were delivered at a rate synchronized with the patient's electrocardiogram; that is, shock waves were fired only during the refractory period of the ventricular cycle. As a result, the shock wave delivery rate was typically around 60-80 times per minute in most cases. The disadvantages of this slow shock wave delivery rate were longer procedure time and longer exposure to sedation/anesthesia. Electrical artifacts due to patient movement also affected the treatment. [83] In the subsequent development of the second- and third-generation lithotriptors, it was observed that ungating the shock wave delivery from the ECG resulted in few, if any, cardiac complications. [83-85] Currently, in most centers, shock waves are delivered at a rate of about 100-120 shocks per minute.

III The Progress and Current Status of Extracorporeal Shock Wave Lithotripsy

The introduction of ESWL in the early 1980s, with an excellent success rate of more than 90%, revolutionized the treatment of urinary calculi. The initial success of the HM-3 led to rapid development of the technology, which resulted in different second-generation lithotriptors coming onto the market, [77] including the Siemens Lithostar, Wolf Piezolith 2300, and Dornier MPL 9000, among others. [86] The main objectives in the development of this generation of lithotriptors were to improve the technology of lithotripsy and patient management. As mentioned in the previous section, various new generator and focusing mechanisms, dry coupling, and different imaging systems were demonstrated to be feasible and clinically applicable. These modifications and the introduction of piezoelectric lithotripsy also helped to improve patient management, through dry coupling and relatively pain-free treatment. Although these second-generation lithotriptors fulfilled the objectives to various degrees, studies show that the efficacy of these machines did not meet the standard set by the HM-3. [87-90] The stone-free, auxiliary procedure, and retreatment rates were all higher than those reported for the original HM-3.

Further modifications were made to lithotriptor design, resulting in the third-generation machines. These machines are characterized by a wider range and higher energy output to improve the efficacy of treatment, a combined localization system (both ultrasound and fluoroscopy) for wider range of clinical usage, and the integration of the shock wave source and localization system with an endoscopic table (the workstation concept) to improve the utility of the machine. [86] However, the efficacy of these latest lithotriptors still does not reach that of the HM-3. [91-94] Morevoer, the rapid improvements in endoscopic technologies would continuely challenge the role of ESWL in stone management.[80, 81, 95]

Currently, the main limitation of ESWL is the low treatment successful rate and high retreatment / auxiliary procedure rate, compared to other endoscopic treatment. Therefore, there are several approaches attempted to improve its treatment outcomes, including better patient selection, better treatment protocol and also better machine design.

Despite the initial enthusiasm for ESWL as a treatment method for all urinary calculi, accumulated experience suggests that it does have certain limitations. For example, simple stone parameters, like larger stone size, lower caliceal stone, cystine stones, will lead to poorer treatment outcomes. But there are many other factors that can affect the treatment outcomes. Therefore, identifying these parameters, either clinical or imaging, will help to improve patient selection and optimize the application of ESWL.

In addition to improvement of patient selection for treatment, modification of treatment protocols may also help to improve the results and minimizing complications. In the past, much effort was concentrated in the improvement in machine design, with less effort put into the improvement of treatment protocol. But recently, investigators have awared that treatment protocols will also affect the treatment result significantly. In fact, improving the treatment protocol maybe a simpler and more economical way to improve treatment result than purchasing new machines. Currently, potential areas that are being investigated included analgesic protocol, shockwave delivery rate, the application of gel for shockwave coupling etc. Hopefully, the results of these studies may help to improve the treatment outcomes of exiting machines.

Lastly, improvement in lithotriptor technology will hopefully improve the treatment result. Newer machine design included machine with wider focal zone, twin head lithotriptors, generator with combined shockwave generation sources etc. Also improvement in imaging for localization of stone and continue monitoring of stone may help to improve the targeting of stone during treatment. However, the main problem in facing these new machine designs is lack of good clinical trial and assessment approach to assess the true impact of these developments in clinical management. As a result, the improvement in machine design, as well as assessment approach are both critical for the continue development of ESWL.

Therefore, despite the current status of ESWL seems to be not as good as one expected, the continue improvement in machine design, treatment protocol, patient selection and assessment mean will help to optimize the performance of lithotriptors and maintain ESWL as the first line treatment for renal stones.

Section 3

Research on Extracorporeal Shock Wave Lithotripsy

Chapter 5

Hypotheses and Objectives

I Summary of the Background

The incidence of upper tract urinary calculi, a common disease in affluent and developed countries, is expected to rise in Hong Kong and mainland China. As the majority of patients who suffer from the disease are males aged 30-60 years, normally the most important years of one's career, the potential loss in terms of socioeconomic productivity should not be underestimated. Effective management of urolithiasis is thus vital for both health care and the economy. Further improvement in the understanding of the disease and its management will benefit both patients and society.

With the development of extracorporeal shock wave lithotripsy (ESWL) and advances in endoscopic techniques in the past two decades, urologists can now manage stones in any part of the urinary tract with minimal complications. The minimally invasive nature of ESWL and short recovery time are especially beneficial for patients. However, despite the early success of ESWL, the performance of the latest machines has never been as good as that of the first-generation machine, the HM-3 lithotriptor. [90, 92] Given the constant improvement in endoscopic techniques, [80,95,96] ESWL technology and treatment strategies need to be improved in order that ESWL may maintain its key role in urinary stone management.

There are several approaches to improving ESWL treatment outcomes, including better patient selection. One potential factor that has been neglected is patient age. In an early report that assessed the prognostic factors for the treatment outcome of the HM-3 for renal stones, patients aged > 60 years had the poorest stone-free rate (SFR) of all age groups. [97] However, there was little follow-up discussion of this observation. Therefore, the effect of patient age on ESWL treatment outcomes is an area worthy of further investigation.

Imaging has an important role in the management of urolithiasis. It can help in the diagnosis and assessment of renal function, planning of treatment, and so forth. New imaging techniques have helped in the further improvement of stone management. For example, non-contrast computerized tomography (NCCT) has gradually replaced intravenous urography as the first-line diagnostic tool for patients with acute loin pain because of its easy availability, fast performance, and high accuracy. [98] In addition to its role in the diagnosis of ureteric stones, NCCT can provide other useful information that may help in predicting the treatment outcome of ESWL and selecting suitable patients for ESWL.

Lower caliceal stones are known to have treatment outcomes poorer than those of stones in other sites in the kidneys. One proposed explanation for this is the anatomical configuration of the lower caliceal collecting system, which hinders the passage of stone fragments. [99] Despite vigorous efforts to identify possible predictive anatomical factors, including infundibular length, caliceal pelvic height, and infundibulopelvic angle, [100-102] no general consensus has been reached regarding the utility of these measurements. This may be due in part to differences in the definition of each factor and inter-observer variation. One aspect that has not been properly addressed is the confounding effect of the different lithotriptors used in different studies, which could limit the generalizability of their results. Therefore, it would be beneficial to assess the effects of different lithotriptors on the applicability of the aforementioned anatomical factors in the prediction of treatment outcomes.

In addition to improvement of patient selection for treatment, modification of treatment protocols may help to improve the results. As mentioned, with the HM3 lithotriptor, general anesthesia was almost always necessary. Nowadays, however, most patients receive simple analgesia and sedation when undergoing lithotripsy. Although the avoidance of general anesthesia is undoubtedly beneficial to patients, there is speculation that less potent analgesic methods may jeopardize treatment outcomes. [103] Further studies could help to assess the effect of pain control on treatment outcomes.

Lastly, continuous development of lithotriptor technology is essential to further improve ESWL treatment outcomes. However, to assess the true impact of the new technologies on treatment outcomes, we need a better approach for comparison of the performance of the different lithotriptors. Although a randomized, controlled trial is the ideal approach, in real clinical practice, this may not be feasible. The proposed use of the effectiveness quotient (EQ), which involves the stratification of treatment outcomes according to stone size and location, controls only for these two factors, and the interpretation of the results is not easy. [104] Therefore, new approaches for the comparison of various new lithotriptors are crucial for the future development of ESWL.

II Thesis Hypotheses

Based on the abovementioned knowledge, a series of studies was planned with the aim to improve our current knowledge of ESWL and hence the treatment outcomes. The hypotheses tested in the studies are as follows.

1. Patient age may be a predictor of ESWL treatment outcome.
2. The parameters measured by NCCT may help in predicting treatment outcomes after ESWL for upper ureteric stones.
3. The mixed findings on the applicability of lower caliceal anatomical factors in predicting the treatment outcome of ESWL for lower caliceal stones may be related to the effects of different lithotriptors.
4. Analgesic consumption during ESWL may affect the treatment outcome.
5. The use of different statistical methods or models may help in comparing the treatment outcomes among different lithotriptors.

III Objectives

1. To assess the effect of patient age on the stone-free rate (SFR) after ESWL for urinary calculi.
2. To assess the predictive ability of various parameters measured by NCCT of the SFR after ESWL for upper ureteric stones.
3. To assess the applicability of caliceal pelvic height (CPH) in the prediction of lower caliceal stone clearance in patients treated with three different lithotriptors within one center.
4. To assess the effect on treatment outcome of the additional usage of intravenous analgesia during ESWL.
5. To demonstrate the feasibility of the use of two different statistical approaches, logistic regression and matched-pairs analysis, in comparing the treatment results among different lithotriptors.

Section 4

Experimental Studies

Chapter 6

The Effect of Age on the Treatment Outcome of Shock Wave Lithotripsy

Abstract

Objective

To investigate the effect of patient age on the stone-free rate (SFR) of patients with urinary calculi treated with shock wave lithotripsy (ESWL).

Materials and Methods

Two thousand one hundred and ninety-two adult patients with solitary, radio-opaque urinary stones 5-15 mm in size, who had received primary ESWL, were identified. Patients were divided into three groups according to their age: ≤ 40 (579), 41-60 (1026), and > 60 (587). Multiple logistic regression was used to assess the effect of age and other possible predictive factors, including patient gender, stone characteristics (side, site, and size), and type of lithotriptor used, on the SFR three months after treatment.

Results

The overall adjusted odds ratios (AORs) for the SFRs of the 41-60 and > 60 age groups (with the ≤ 40 age group as the reference) were 0.708 (0.573, 0.875) ($p = 0.001$) and 0.643 (0.506, 0.818) ($p < 0.001$), respectively. However, when the patients were divided into renal and ureteric stone subgroups, only the SFR after treatment for renal stones was affected by age. The AORs for patients with renal stones for the 41-60 and > 60 age groups were 0.665 (95% CI 0.512, 0.864) ($p = 0.002$) and 0.629 (95% CI 0.470, 0.841) ($p = 0.002$), respectively. Aging had no effect on the SFR after treatment for ureteric stones.

Conclusion

The SFR after shock wave lithotripsy for renal stones, but not ureteric stones, was significantly lower in older patients. Further studies of the effects of aging on renal stone clearance after shock wave lithotripsy are needed to improve stone management in the elderly population.

I Introduction

Despite the initial enthusiasm to use ESWL to treat all urinary calculi, accumulated experience suggests that this treatment method has limitations. A recent study found that elderly patients had a poorer stone fragmentation rate after ESWL.[105] However, the effect of aging on ESWL treatment outcome was not discussed in detail. Therefore, factors that may affect the stone-free rate (SFR) of patients treated by ESWL were reviewed, with special attention paid to the effect of patient age on the outcome parameters.

II Materials and Methods

The treatment records of adult patients (age ≥ 18 years old) with solitary radio-opaque urinary stones 5-15 mm in size who had received primary ESWL between January 1992 and June 2002 were retrieved from a prospectively collected computer database. The database was started with the establishment of our center in 1987, with data collected immediately after ESWL and during follow-up of the patients by the staff. During the study period, patients were treated by one of three lithotriptors, the Wolf Piezolith 2300 (Richard Wolf, Germany), Dornier MPL 9000 (Dornier MedTech, Germany), or Dornier Compact Delta (Dornier MedTech, Germany). Only patients with stone status available at three months after ESWL were included in the study. Patients with ureteric stents or percutaneous nephrostomy tubes were excluded in the analysis. Patient demographic data, stone characteristics, treatment details, and treatment outcomes were then analyzed. The primary outcome parameter assessed was the SFR three months after one session of treatment, which was defined as absence of evidence of stone material by plain radiography or ultrasonography done at three months or earlier after ESWL. In this cohort of patients, routine post-treatment radiography was done to assess whether or not there was fragmentation immediately after treatment. The relationship between fragmentation success and patient age was also analyzed.

The treatment protocols for the MPL 9000 and Compact Delta were quite similar. Patients treated by these two machines were given oral diclofenac as premedication. Additional intravenous fentanyl was used if the patients experienced pain during treatment. During treatment by these machines, the energy level was gradually stepped up according to the tolerance of the patient. For the Piezolith 2300, because the treatment was relatively less painful, no routine pretreatment analgesia was given, and the maximum power level (level 4) was used for all patients. Very occasionally, diclofenac was given to patients when they experienced pain during treatment. Treatment was aimed at a maximum of 4000 shocks for the Piezolith 2300 and Compact Delta and 1500 shocks for the MPL 9000, or until the stone became difficult to visualize or the patient could not tolerate further treatment.

Analysis was performed using SPSS 14.0 for Windows (SPSS Inc, Chicago, Illinois). Simple and multiple logistic regression were performed for all of the potential predictive factors for the SFR at three months and fragmentation success. Potential predictive factors included patient age and gender, stone side, size, and site, and type of machine used. Patients were grouped into three groups according to age, ≤40, 41-60, and >60 years old, with the ≤40 age group used as the reference category. Stone size was entered as a continuous variable. In the evaluation of the effect of stone location by multiple logistic regression, stone locations were chosen as reference categories if they were found to be about average with respect to the outcome during univariate analysis. For the effect of machine used, indicator variables were created for the Piezolith 2300 and MPL 9000 (the Compact Delta was used as the reference category). All covariates were entered into the multivariate model regardless of their significance level in the univariate model. Backward stepwise selection was used for the selection of the final multivariate logistic regression model.

III Results

Two thousand four hundred and eighty-nine patients with solitary radio-opaque urinary stones 5 to15 mm in size received primary ESWL from January 1992 to June 2002. The follow-up information of 297 (11.9%) patients was incomplete and thus the records of only 2192 patients were available for analysis. Among these patients, 1498 (68.3%) had renal stones and 694 (31.7%) had ureteric stones. Their mean age was 50.6 years old (ranging from 18 to 97 years old). Of patients, 579 (26.4%) were aged 40 or less, 1026 (46.8%) were 41-60, and 587 (26.8%) were more than 60. The characteristics of patients in each age group are listed in Table 6.1. The stone distribution among the different age groups was comparable. However, there was a gradual increase in the mean stone size across the age groups.

The treatment parameters for each age group are listed in Table 6.2. Among the three age groups, the proportion of patients treated by each machine was not exactly the same. The percentages of patients treated by the MPL 9000 were similar among the different groups, but more elderly patients were treated by the Piezolith 2300 and more young patients were treated by the Compact Delta. The number of shocks received and energy level used for the different age groups are also listed for each machine. The parameters for the Piezolith 2300 and MPL 9000 were similar among the three age groups. However, for the Compact Delta, a higher energy level was used in the older populations. The percentage of patients in each group that did not have complete follow-up information was 10-13.1%. Plain radiography was used in the majority of the patients for the assessment of treatment outcome.

The SFRs and stone fragmentation rates for the overall population and individual age groups are listed in Table 6.3. The overall SFR at three months was 44.5%. The SRFs of the ≤ 40, 41-60, and > 60 age groups were 54.0%, 43.0%, and 37.6%, respectively. Both the SFR and fragmentation rate were lower in the older population.

As the stone characteristics of each age group were not the same, multivariate analysis was used to assess the effects of individual predictive factors on the outcome. The overall adjusted odds ratios (AORs) for the SFRs at three months are given in Table 6.4. Younger age, smaller stones, left-side stones, and patients treated by the MPL 9000 or Piezolith 2300 were factors associated with a significantly better SFR. Patients with lower caliceal stones had a significantly lower SFR. The results indicate that patient age was a significant factor for the SFR, with patients more than 60 years old having the worst results. However, when the patients were divided into renal and ureteric stone subgroups, age affected the SFR of renal stones but not that of ureteric stones. The AORs for renal stones in patients in the 41-60 and > 60 age groups (with the ≤ 40 age group as the reference) were 0.665 (95% confidence interval: 0.512, 0.864) ($p = 0.002$) and 0.629 (95% confidence interval: 0.470, 0.841) ($p = 0.002$), respectively.

Regarding post-treatment fragmentation, the percentages of patients with evidence of fragmentation of the overall population, renal stone subgroup, and ureteric stone subgroup were 81.3%, 87.2%, and 73.2%, respectively. The fragmentation rates of the overall population and renal and ureteric stone subgroups according to age group, after adjusted for renal stone size, stone side and machine used, are listed in Table 6.5. In the overall assessment, patients older than 60 years old had significantly poorer stone fragmentation than had the other age groups. However, in the subgroup (renal and ureteric stone subgroups) analysis, a tendency towards a lower fragmentation rate for renal stones was also observed in those patients more than 60 years old, but this result was not statistically significant.

IV Discussion

The results of this study showed that patient age was a significant predictive factor for the SFR after ESWL for renal stones – the older was the patient, the lower was the SFR. Larger stone size, lower caliceal stones, and right-side stones were other pretreatment factors that were associated with a significantly lower SFR.

Although numerous studies have addressed the various factors that affect the clinical outcome of ESWL, patient age is included only infrequently in the analysis. In an early report assessing the prognostic factors for the treatment outcome of the HM-3 (Dornier MedTech, Germany) for renal stones, patients more than 60 years old were found to have the poorest SFR among all age groups. [97] In a recent study, 3023 patients with urinary calculi (both renal and ureteric calculi), were divided into four age groups, and the results showed that older patients were associated with a significantly poorer SFR. [106] In a report on 2954 patients with renal (not ureteric) stones who were treated by ESWL, multivariate analysis showed that patients older than 40 years old had a significantly poorer SFR.[107] However, in another report on ureteric stones by the same group of urologists, analysis using either artificial neural networks or logistic regression models showed that patient age was not a significant factor for the treatment outcome. [108] Delakas et al. analyzed the treatment outcomes of 688 patients with ureteric stones and again, patient age was not a significant predictor for treatment success. [109] The results of this study indicated that patient age was a significant outcome predictor for the overall population and renal stone subgroup but not the ureteric stone subgroup. A separate analysis of the same data set used in this study with patient's age considered as a continuous variable was also performed.

(Data and results were not shown here) In this analysis, the same relatioship, increasing age was a negative factor for stone free rate, was again observed. These findings are in keeping with the abovementioned findings: age affects the treatment outcome of renal stones but not that of ureteric stones. What is responsible for this observed difference in the effect of age on the outcome of ESWL?

Ikegaya et al. observed that the stone fragmentation rate was poorer in the elderly population. [105] In this study, in the analysis of the immediate post-treatment stone fragmentation rate of the overall population, patients more than 60 years old were also observed to have a poorer fragmentation rate. In the subgroup analysis, a tendency towards a lower fragmentation rate for renal stones was observed in those patients more than 60 years old, but this result was not statistically significant. Taken together, the findings suggest that among elderly patients, ESWL for renal stones might yield a poorer fragmentation rate, which in turn will result in poorer treatment outcomes.

The reason for the possibly poorer fragmentation rate for renal calculi in the elderly population is unknown as yet. This poorer rate is unlikely to be related to any change in the composition of the stones; otherwise, both renal and ureteric stones would be affected. However, it might be related to the effectiveness of the transmission of shock wave energy to the targeted stone. The main difference between the shock wave path for renal stones and that for ureteric stones is that in the former case, the shock wave needs to pass through the kidney parenchyma before reaching the stone. It is well known that aging results in sclerotic change in the kidneys. [110, 111] Such change could affect the acoustic impedance of kidneys, which is indicated by the changes in the echogenicity of kidneys revealed by ultrasonography. This change in the acoustic impedance of aging kidneys is believed to be one of the reasons for the lower efficacy of shock wave transmission and hence lower fragmentation and stone-free rates for renal stones. Because of the retrospective nature of this study, the renal function of the patients, in particular the individual kidney differential function, was not available. Therefore we could not further verify our hypothesis about the effect of age related sclerotic changes, which may reflect on the renal function, on treatment outcomes. As a result, further studies are needed to confirm this postulation.

Another possible reason for the lower SFR in the elderly population is the possibility of change in pyeloureteric motility secondary to aging. In the literature, there is no evidence that suggests that aging affects pyeloureteric motility, and the findings of intravenous urography and dynamic radioisotope studies indicate no clinically significant difference in the drainage of contrast or isotopes between different age groups. However, this could be an area that warrants further examination.

This study may be criticized for not having enough power to show the effect of patient age on the treatment outcome of ESWL for ureteric stones. However, the results are consistent with the findings in the literature, and in agreement with those of the effect of age on the success of renal stone treatment.

Another possible criticism is the use of plain radiography for the assessment of treatment outcome. The use of plain radiography (included tomography) inevitably results in overestimation of the SFR when compared with non-contrast computerized tomography (NCCT). Based on studies comparing the sensitivity of plain radiography and NCCT in diagnosing ureteric stone during ureteric colic, the diagnostic rate were 50-60% and above 90%, respectively. [178-180] The sensitivity of plain radiography will expect to be even lower for small stone fragments. However, NCCT was not a standard practice in our center during the study period (1992-2002), and we relied on plain radiography for the assessment of treatment outcomes. As most of the patients were assessed by the same radiographic method, this overestimation of the SFR should not affect the interpretation of the results.

As ESWL in elderly patients has lower success rates, one could try offering more treatment sessions to improve outcomes. However, ESWL in the elderly population is not without complications. Janetschek et al. reported that there was more new onset of hypertension in patients more than 65 years old after ESWL. [112] Dhar et al. reported that elderly patients had a higher chance of subscapsular or perinephric haematoma after ESWL by electromagnetic lithotriptors, which is the most commonly used generator design in modern lithotriptors. [113] In clinical practice, ESWL is frequently used as the first line of treatment for the elderly to avoid the invasiveness and potential complications of endoscopic treatment and anesthesia. However, with the improvements in technique and instruments, the risk of modern endoscopic stone procedures is minimal. For ureteroscopy, the use of a small caliber endoscope and holmium laser lithotripsy has decreased significantly the complication rate, to less than 1%. [114] Although the need for regional or general anesthesia is one of the criticisms of ureteroscopy as opposed to ESWL, there are reports of the successful use of local anesthesia and intravenous sedation for ureteroscopy. [115] Another study found that the complication rate of percutaneous nephrolithotomy for the elderly (age > 70 years old) was similar to that for the younger population. [116] Therefore, endoscopic treatment should not be withheld from the elderly, especially when the stones are associated with a poorer ESWL outcome, such as lower caliceal or larger stones.

V Conclusion

The results indicate that patient age is a significant predictive factor for the treatment outcome of ESWL for renal, but not ureteric, stones. Further studies are needed to find possible explanations for this phenomenon. Because of the lower success rate and also the potential short- and long-term complications of ESWL in the elderly population, alternative treatment methods should be considered for urinary calculi treatment in these patients.

Table 6.1 Patient and stone characteristics of each age group

Age group	**≤ 40 years old**	**41-60 years old**	**> 60 years old**	**Total**
Number of patients	579 (26.4%)	1026 (46.8%)	587 (26.8%)	2192 (100%)
Sex				
Male	375 (64.8%)	781 (76.1%)	420 (71.6%)	1576 (71.9%)
Female	204 (35.2%)	245 (23.9%)	167 (28.4%)	616 (28.1%)
Stone site				
Kidney				
Upper caliceal	36 (6.2%)	73 (7.1%)	43 (7.3%)	152 (6.9%)
Mid-caliceal	64 (11.1%)	93 (9.1%)	80 (13.6%)	237 (10.8%)
Lower caliceal	191 (33.0%)	381 (37.1%)	205 (34.9%)	777 (35.4%)
Renal pelvic	76 (13.1%)	155 (15.1%)	101 (17.2%)	332 (15.1%)
Ureter				
Upper ureteric	149 (25.7%)	213 (20.8%)	100 (17.0%)	462 (21.1%)
Mid-ureteric	7 (1.2%)	14 (1.4%)	9 (1.5%)	30 (1.4%)
Lower ureteric	56 (9.7%)	97 (9.5%)	49 (8.3%)	202 (9.2%)
Side				
Right	334 (57.7%)	597 (58.2%)	342 (58.3%)	1273 (58.1%)
Left	245 (42.3%)	429 (41.8%)	245 (41.7%)	919 (41.9%)
Stone size				
Size subgroups				
5-10 mm	461 (79.6%)	771 (75.1%)	400 (68.1%)	1632 (74.5%)
11-15 mm	118 (20.4%)	255 (24.9%)	187 (31.9%)	560 (25.5%)

Table 6.2 Treatment parameters and follow-up methods for patients in each age group (KUB – plain radiograph, US – ultrasound)

Age group	≤ 40	41-60	> 60
Number of patients	579 (26.4%)	1026 (46.8%)	587 (26.8%)
Treated by			
Wolf Piezolith 2300	255 (44.0%)	521 (50.8%)	297 (50.6%)
Dornier MPL 9000	147 (25.4%)	215 (21.0%)	135 (23.0%)
Dornier Compact Delta	177 (30.6%)	290 (28.3%)	155 (26.4%)
Wolf			
Mean/Median no. of shocks	3063/3000	3219/3000	3315/3500
MPL 9000			
Mean/Median no. of shocks	1394/1206	1456/1300	1445/1300
Mean kV	19.66	20.08	19.94
Compact Delta			
Mean/Median no. of shocks	3236/3500	3339/3500	3163/3400
No. (%) of patients at power setting ≤ 3	71 (40.3%)	99 (34.3%)	54 (35.5%)
No. (%) of patients at power > 3	105 (59.7%)	190 (65.7%)	98 (64.5%)
Follow-up			
Loss follow-up (% of total patients)	87 (13.1%)	144(12.3%)	66 (10.0%)
Outcome assessed by KUB	576	1019	580
Outcome assessed by US alone	2	6	3
Outcome assessed by KUB and US	1	1	4

Table 6.3 Stone-free rate at three months post treatment and stone fragmentation rate for the overall population and renal and ureteric stone subgroups in each age group

Age	Renal stone	Ureteric stone	Total
	Number of patients (% of total) Stone-free rate/ Fragmentation rate	Number of patients (% of total) Stone-free rate/ Fragmentation rate	Number of patients Stone-free rate/ Fragmentation rate
≤ 40 years old	367 (63.4%)	212 (36.6%)	579
	53.4%/93.7%	55.2%/75.9%	54.0% / 84.3%
41-60 years old	702 (68.4%)	324 (31.6%)	1026
	40.9% / 86.8%	47.5% / 73.8%	43.0% / 82.7%
> 60 years old	429 (73.1%)	158 (26.9%)	587
	40.6% / 82.3%	41.1% / 68.4%	37.6% / 76.0%
Total	1498 (68.3%)	694 (31.7%)	2192
	43.9% / 87.2%	48.4% / 73.2%	44.5% / 81.3%

Table 6.4 Adjusted odds ratios of various predictor variables for the stone-free rate three months after ESWL (only significant ratios are shown)

	Adjusted odds ratio	95% CI	P value
Age (reference ≤ 40years old)			
41-60 years old	0.708	0.573, 0.875	0.001
> 60 years old	0.643	0.506, 0.818	< 0.001
Stone side (reference left side)			
Right	0.811	0.680, 0.967	0.020
Stone size (mm)	0.860	0.831, 0.890	< 0.001
Machine used (reference Dornier Compact Delta)			
Wolf Piezolith 2300	1.403	1.136, 1.733	0.002
Dornier MPL 9000	1.751	1.258, 2.257	< 0.001
Stone site (refernce to other stone sites besides lower caliceal stone)			
Lower caliceal stone	0.739	0.577, 0.944	0.016

Potential predictors used in the analysis: patient's age and sex, stone side, stone site, stone size, machine used.

Table 6.5 Adjusted odds ratio (AOR) of the immediate post-treatment fragmentation rate for the different age groups (with $\leq$ 40 years old as the reference group)

Age group	Overall		Renal stone		Ureteric stone	
	AOR (95% CI)	P value	AOR (95% CI)	P value	AOR (95% CI)	P value
41-60 years old	0.991 (0.743, 1.322)	0.951	0.984 (0.655, 1.477)	0.936	1.049 (0.697, 1.579)	0.819
> 60 years old	0.727 (0.530, 0.999)	0.049	0.716 (0.465, 1.103)	0.130	0.774 (0.485, 1.236)	0.284

Factors adjusted including stone side, stone size and machine types

Chapter 7

The Use of Non-Contrast Computerized Tomography Measurements in Predicting the Treatment Outcome of Shock Wave Lithotripsy

Abstract

Objective

To investigate the role of non-contrast computerized tomography (NCCT) in predicting the treatment outcome of extracorporeal shock wave lithotripsy (ESWL) for upper ureteric stones and hence to formulate a clinical algorithm to facilitate the clinical management of such stones.

Materials and Methods

Adult patients with upper ureteric stones confirmed by NCCT and scheduled for primary in situ ESWL were prospectively recruited. Standardized treatment was performed on each patient. The primary endpoint was the stone-free rate at three months. Pretreatment NCCT was assessed by a single radiologist blinded to the clinical parameters. The predictive values of the CT measurements for the treatment outcome were then assessed.

Results

Between October 2004 and July 2007, 94 patients (60 males and 34 females) were recruited for the study. Logistic regression showed that stone volume, mean stone density, and skin-to-stone distance were potential predictors of successful treatment. Receiver operating characteristic (ROC) curve analysis showed that the optimal cutoff points for predicting treatment outcome for stone volume, mean stone density, and skin-to-stone distance were 0.2 cc, 593 Hounsfield units (HUs), and 9.2 cm, respectively. A simple scoring system based on these three factors, stone volume < 0.2 cc, mean stone density < 593 HUs, and skin-to-stone distance < 9.2 cm, was constructed. The stone-free rates (SFRs) for patients having either 0, 1, 2, or 3 factors

were 17.9%, 48.4%, 73.3%, and 100%, respectively (linear-by-linear association test = 22.83, $p < 0.001$).

Conclusion

Stone volume, mean stone density, and skin-to-stone distance were potential predictors of the successful treatment of upper ureteric stone with ESWL. A scoring system based on these three factors can help to separate patients into different outcome groups and facilitate treatment planning.

I Introduction

Ureteric colic due to an upper ureteric stone is a common urological problem. Traditionally, intravenous urography has been the gold standard in the diagnosis of ureteric stones. However, non-contrast computerized tomography (NCCT) has gained popularity and become the new standard for diagnosis. [98]

Although many treatment options are available, ESWL has remained one of the first-line treatments for upper ureteric stones. [117] The advantages of ESWL include its simplicity and non-invasiveness. However, the main drawback of ESWL, as compared with ureteroscopy, is its lower stone-free rate. [118] Unsuccessful treatment results in prolonged ureteric obstruction and hence further suffering of patients. If one could identify the favorable factors underlying successful ESWL, then a better treatment plan could be formulated. There are many simple factors that may affect treatment outcome, including stone size, site, and multiplicity. [119] Recently, there has been increasing evidence that various NCCT parameters can predict ESWL treatment outcome, including mean stone density (MSD, measured by Hounsfield units), stone volume (SV), skin-to-stone distance (SSD), and the microstructure of the stones, among others. [120-125] (Table 7.1) If decision guidelines could be formulated from these factors, then better treatment plans could be devised for patients.

Therefore, a prospective study was performed to determine the factors that affect the outcome of ESWL for upper ureteric stones and formulate clinical guidelines to facilitate future patient management.

II Materials and Methods

Adult patients (age $\geq$ 18 years old) with radio-opaque upper ureteric stones diagnosed by NCCT and for whom primary ESWL was planned were recruited into the study. An upper ureteric stone was defined as a stone located in the ureter proximal to the upper border of the sacroiliac joint on plain radiography. Exclusion criteria included patients with contraindications for ESWL, including pregnancy, active urosepsis, or coagulopathy, patients with percutaneous nephrostomy or ureteric stenting, and suspected distal ureteric obstruction.

Informed consent was obtained from each patient, and background information was collected prior to treatment. All patients were treated with the Sonolith 4000+ (Technomed, France) with a standard protocol. They all received prophylactic antibiotics and an intravenous injection of alfentanil 0.5 mg as premedication. Shock waves were delivered at an asynchonized rate of 100 shocks per minute or using ECG triggering with a power of 80-90%. The positioning of the stone was checked by fluoroscopy after every 1000 shocks. Treatment was stopped after a maximum of 3000 shocks, or if the stone could not be located or the patient could not tolerate the procedure. After ESWL, an x-ray follow-up was done at two weeks, six weeks, and three months to assess the progress. All follow-up x-ray films were assessed by a single urologist, who was blinded to the NCCT information. Plans for further management, including observation, repeat ESWL, or other auxiliary procedures, were decided based on the x-ray findings, with the patient's benefit as the sole factor considered. Stone clearance was further documented by intravenous urography in all patients.

All pretreatment NCCT was performed with a multidetector row CT scanner at 120KV and 150mA, with 4 cm collimation and 0.625 mm slide thickness. The CT scans were reviewed by a single radiologist who was blinded to the clinical results. Information on stone factors such as stone volume (SV), mean stone density (MSD), stone level, the "rim sign" around the stone, and skin-to-stone distance (SSD) was measured. The radiologist also attempted to classify the internal structure through different viewing windows into hyperdense center, hypodense center, and homogeneous. [126] Stone level was defined as the vertical distance of the center of the stone from the upper border of the pubic symphysis. The rim sign was used to reflect any tissue reaction around the stone. SSD was defined as the vertical distance from the center of the stone to the skin, measured on a supine NCCT film. (Figure 7.1)

The primary outcome of the study was the stone-free rate (SFR) three months after one ESWL session. Stone-free status was defined as no radio-opacity detected on a good-quality plain radiograph and confirmed by intravenous urography. The crude odds ratio was calculated to investigate the effect of possible independent factors on the outcome, and the adjusted odds ratio (AOR) was then obtained after controlling for confounders using backward stepwise logistic regression. Because of possible interaction between SV and the measurement of MSD, [127] the confounding effect between SV and MSD was also assessed.

Receiver operating characteristic (ROC) curves were plotted to obtain the optimal cutoff points for significant predictors for treatment outcome. Backward stepwise logistic regression was then reperformed with these factors regrouped according to the ROC curves to develop a clinical algorithm. All of the statistical analysis was performed using SPSS 14.0 with a significance level of 0.05.

III Results

Between October 2004 and July 2007, 94 patients (60 males and 34 females) with a mean age of 52.4 years (range: 24-94 years) were recruited. The patient and NCCT stone characteristics are summarized in Table 7.2. The treatment parameters for the patients are listed in Table 7.3. Successfully treated stones received significantly fewer shocks, a lower energy level, and less total energy. This was probably related to the protocol, that is, treatment was stopped once the stone was not detectable, so fewer shocks and less total energy were given to these successfully treated stones. The overall complication rate for ESWL was quite low (2.13%). One patient developed steinstrasse that required ureteroscopy and another patient developed vomiting shortly after ESWL, which subsided within a few hours after treatment. Only six patients were able to retrieve a sufficient number of stone fragments for stone analysis. All of these fragments were a mixture of calcium oxalate (69-92% of stone composition) and calcium phosphate (8-31% of stone composition).

The overall SFR was 50% (47/94). Univariate analyses showed that a greater SV (OR = 0.028; 95% CI 0.003, 0.234; p = 0.001) and a greater MSD (for every 10-unit increase in MSD, OR = 0.932; 95% CI 0.932, 0.971; p = 0.001) were associated with a lower likelihood of success (Table 7.4). Logistic regression was used to assess the effect of all potential predictive factors, including age, sex, BMI, SV, stone level, MSD, SSD, stone level, and rim sign. Because of the interaction between SV and the measurement of MSD (Figure 7.2), the confounding effect was adjusted by adding interaction parameters between SV and MSD in the analysis. [127] The results showed that greater SV (OR = 0.89; 95% CI 0.10, 0.89; p = 0.033) and MSD (for every 10-

unit increase in MSD, OR = 0.947; 95% CI 0.9, 0.996; p = 0.035) were significant predictors of a lower SFR. The SFR was marginally smaller for a longer SSD (OR = 0.716; 95% CI 0.492, 1.041; p = 0.08). There was no significant association between the interaction parameters of MSD and SV on the outcome (OR = 1.013; 95% CI 0.922, 1.033; p = 0.226). (Table 7.4)

The ROC curves of these factors were plotted to find the optimal cutoff points to develop an algorithm to predict the treatment outcome of ureteric stones treated with ESWL. These points were found to be SV at 0.2 cc, MSD at 593 HUs, and SSD at 9.2 cm. The area-under-curve for SV, MSD and SSD were 0.755, 0.728 and 0.544, respectively.

The variables SV, MSD, and SSD were then regrouped into dichotomous variables based on the ROC curves, and logistic regression of these factors was performed to test their strength in predicting the ESWL outcome. The adjusted odds ratios (AORs) for SV ≤ 0.2 cc vs. SV > 0.2 cc, SSD ≤ 9.2 mm vs. SSD > 9.2 cm, and MSD ≤ 593 HUs vs. MSD > 593 HUs for the SFR were 4.297 (95% CI 1.422, 12.985; p = 0.01), 3.497 (95% CI 1.073, 11.2391; p = 0.038), and 3.388 (95% CI = 1.154, 9.941; p = 0.026), respectively. (Table 7.5) Attempts have been made to try to round up the cut-off value to more user friendly figures, for MSD to 600 HU and SSD to either 9 or 10mm. But in logistic regression analysis, both factors became not statistically significant and so the original cut-offs (593HU and 9.2mm respectively) were kept for algorithms construction.

An algorithm of these factors with equal weighting was formulated. (Table 7.6) The SFRs at three months for scores 0, 1, 2, and 3 were 17.9%, 48.4%, 73.3%, and 100%, respectively (chi square test, $p < 0.001$; linear-by-linear association test = 22.83, $p < 0.001$).

IV Discussion

The results revealed that SV, MSD, and SSD are significant predictors for successful ESWL. Based on these factors, a scoring system was formulated to stratify the treatment outcomes of patients with upper ureteric stones. The SFRs at three months for scores 0, 1, 2, and 3 were 17.9%, 48.4%, 73.3%, and 100%, respectively ($p < 0.001$). This practical information is important for future pretreatment counseling and treatment plan formulation for patients with upper ureteric stones.

There is increasing evidence to suggest that stone measurement by NCCT can help in predicting treatment outcome of ESWL. However, practical guidance on its usage is still scanty. Therefore, it is hoped that this study can help to generate practical guidelines. Although there have been many publications in the literature reporting on the analysis of NCCT for the diagnosis of renal stones (Table 7.1), the clinical application is still not universal. [119] However, the application of NCCT in the case of ureteric colic/ureteric stones is relatively well established and is a common practice worldwide. [98, 128] Therefore, it was decided in this study to recruit only those patients who were confirmed by NCCT to have upper ureteric stones. As a result, the findings are more applicable to centers that use NCCT for the diagnosis of ureteric stones. Patients with renal stones were also excluded because the treatment outcome of renal stones can be affected by additional factors, such as age [129] and lower caliceal anatomy. [99] All of these factors must be controlled for during statistical analysis, which makes the situation more complicated than the case of analyzing only ureteral stones. After identifying the predictors of successful treatment, practical guidelines were formulated to facilitate future patient management. Therefore, in the future, when a patient presents with ureteric colic, after the diagnosis is confirmed by NCCT, the success rate of treating with ESWL can also be estimated. This could facilitate decision making, and hopefully, prevent unnecessary delays and suffering due to failed stone clearance after ESWL.

Other preoperative practical guidelines are available in the literature. Kanao et al. [119] conducted a prospective study to assess the treatment outcomes of more than 500 stones, both renal and ureteral. Using logistic regression, stone length, location, and number were identified as significant predictors for treatment success. A nomogram was then formulated. The methodology of this study was similar to that of Kanao et al.; however, only patients with solitary proximal ureteric stones were recruited prospectively for analysis, and NCCT was also used to provide more accurate measurement of stone size (stone volume) and other parameters. Kacker et al. reported another practical guideline to facilitate patient selection for ESWL. [130] In their retrospective study, the authors preselected several parameters, including maximum, average, and standard deviation of stone attenuation, stone size, and SSD, as potential radiographic parameters of interest. These parameters were then measured in 325 stone cases. The ROC curves for each parameter were plotted and average attenuation was selected as the parameter of interest. Using statistical calculation, together with the results of Kanao et al., a refined probability of treatment success was calculated. [119] The authors concluded that ESWL was effective in treating solitary stones 6-10 mm in size, with an average stone attenuation of less than 1000 HUs (for proximal ureteral stones) and less than 640 HUs (for renal pelvis stones). However, the retrospective nature and complicated statistical calculation of this study were drawbacks. A summary of the comparison of these two studies with our study is given in Table 7.7.

Of the three predictors identified in this study, MSD is the one most commonly identified in the literature. [120-125] However, it has also been observed that MSD measurement is affected by stone size, [127] which we also observed. (Figure 7.2) Therefore, multivariate analysis in this study included the assessment of the potential interaction between these two factors. This could help to control for the confounding effect of SV on MSD measurement and also in the assessment of the strength of the interaction. However, the results showed that the interaction between SV and MSD was not a significant predictor of the outcome.

The suggestion of Pareek et al. was not followed in the measurement of SSD in this study, that is, to take the average of three measurements taken at 0^{o}, 45^{o}, and 90^{o} from the stone center to the skin. (Figure 7.1) [121] In the Sonolith 4000+, the generator approaches the patient directly from below rather than from the lateral direction, as in the Doli S lithotriptor. Therefore, a vertical measurement of SSD correlates better with the actual distance of the shock wave path.

The results of this study indicated that BMI was not a significant predictor of treatment outcome, whereas SSD was a marginally significant predictor. This finding is similar to that of Pareek et al. [121] However, El-Nahas et al. found just the opposite, that is, that BMI, not SSD, was a significant predictor of success. [125] I believe that the effect of BMI on ESWL outcome is probably related to the distance of the stone from the skin, which reflects the shock wave path in the body. As body fat distribution varies in different races and sexes, BMI may not truly reflect central body fat distribution, [131] which is probably the main factor affecting SSD. Therefore, SSD is probably a more direct measurement of the effect of body build on ESWL outcome than is BMI.

As the stone treated in our study were ureteric stone, therefore as discussed in previous session, age was again shown to be not a significant predictor for the treatment outcome.

It was initially planned that this study would follow the method suggested by Jacobsen et al. to classify the internal structure through different viewing windows into hyperdense center, hypodense center, and homogeneous center groups to determine the effect of the internal structure on ESWL outcome. [126] However, in the actual study setting, the internal structure of the stone could not be seen well (all patients were classified as homogenous). There have been promising reports of in vitro studies of the applicability of microcomputed tomography in assessing the internal structure of stones for the prediction of ESWL results. [119] However, further clinical studies are needed to clarify its role.

The overall success rate after one session of ESWL was only 50%, which was slightly lower than that of other studies. [118, 119] This could be due in part to there being no real-time fluoroscopic screening during treatment by the Sonolith 4000+. However, with the incorporation of a real-time fluoroscopic system in the latest version of the electroconductive generator, the reported success rate is approaching that of the HM-3 machine. [132]

Finally, the scoring system was tested using only the original data set. It was found to be able to stratify patients according to different success rates; however, further verification of this scoring system with external data is important to confirm its general applicability.

V Conclusion

The results of this prospective study showed that MSD, SV, and SSD, as measured by NCCT, are predictors of successful ESWL for upper ureteric stones. A simple scoring system can be constructed to stratify patients into different prognostic groups. For future patients who present with ureteric colic and suspected upper ureteric stones, NCCT can provide both the diagnosis and an estimated ESWL success rate. This will facilitate the decision process for the patient and hopefully, minimize unnecessary delays in the management of the problem.

Table 7.1 Summary of the main studies of the role of non-contrast computerized tomography stone measurement in treatment outcome

Authors	Number of patients	Stone site	Predictors of successful treatment			
			MSD	SV	SSD	Other
Joseph et al. [120]	30	Renal	Yes	--	--	--
Pareek et al. [121]	64	Lower pole	No	--	Yes	--
Gupta et al. [122]	112	Renal or proximal ureteric	Yes	--	--	--
Yoshida et al. [123]	62	Renal or proximal ureteric	Yes	Yes	--	Hump existence
Perks et al. [124]	76	Renal or ureteric	Yes	--	--	--
El-Nahas et al. [125]	120	Renal	Yes	No	No	

Table 7.2 Patient characteristics and stone parameters measured using non-contrast computerized tomography

	Successful (n = 47)	Unsuccessful (n = 47)	Overall (N = 94)	P value
Patient characteristics				
No. of patients	47	47	94	
Mean age (range)	51.4 (30-82)	53.5 (24-94)	52.4 (24.0, 94.0)	0.424
Sex (%)				
Male	27 (57.4%)	33 (70.2%)	60 (63.8%)	0.200
Female	20 (42.6%)	14 (29.8%)	34 (36.2%)	
Mean BMI (range)	23.67 (17.72-31.81)	24.37 (18.15-36.12)	24.0 (17.72, 36.12)	0.332
Stone parameters				
Mean stone volume (cc)	0.25 (0.07-1.09)	0.50 (0.09-2.11)	0.38 (0.07-2.11)	0.001
Mean stone density (HU)	534 (340-961)	626 (412-842)	580 (340-961)	0.001
Stone level (cm)	18.99 (12.3-23.9)	18.97 (14.5-24.2)	18.97 (12.3-24.2)	0.957
Mean skin-to-stone distance (cm)	10.23 (6.9-13.0)	10.44 (7.7-13.5)	10.34 (6.9-13.5)	0.456
Presence of rim sign (%)				
Yes	33 (70.2%)	30 (63.8%)	63 (67.0%)	1.000
No	14 (29.8%)	17 (36.2%)	31 (33.0%)	
Internal structure				
Homogenous	47 (100%)	47 (100%)	94 (100%)	NA
Hyperdense or hypodense center	0 (0%)	0 (0%)	0 (0%)	

Table 7.3 Treatment parameters for successful and failed cases

Treatment Parameters	Mean (range)			
	Successful (n = 47)	Unsuccessful (n = 47)	Overall (n = 94)	P value
Total no. of shocks	2657 (1000-3000)	2957 (2000-3000)	2807 (1000-3000)	0.002
Energy level (%)	81.28 (70-90)	85.43 (80-90)	83.35 (70-90)	< 0.001
Total energy amount	659.02 (223-812.7)	755.51 (470-819.6)	707.27 (223-819.6)	< 0.001
Dosage of alfentanil (mg)	0.56 (0.5-1.0)	0.54 (0.5-1.0)	0.55 (0.5-1.0)	0.506
Treatment time (min)	47.49 (20-75)	52.47 (35-140)	50.0 (20-140)	0.348

Table 7.4 Univariate and multivariate analysis of patient characteristics and stone parameters for ESWL outcomes

Patient Characteristics	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age (years old)	0.987 (0.956, 1.019)	0.424	*	*
Sex (Male vs. female)	1.746 (0.745, 4.091)	0.200	*	*
BMI (kg/m^2)	0.943 (0.837, 1.062)	0.332		
Stone volume (c.c.)	0.028 (0.003, 0.234)	0.001	0.089 (0.010, 0.819)	0.033
Mean stone density (HU)	0.993 (0.989, 0.997)	0.001	0.995 (0.990, 1.000)	0.035
Stone level (cm)	1.005 (0.853, 1.182)	0.957	*	*
Skin-to-stone distance (cm)	0.895 (0.668, 1.198)	0.456	0.716 (0.492, 1.041)	0.080
Presence of rim sign (No vs. yes)	1.366 (0.564, 3.166)	0.511	*	*

Variables included in the logistic regression analysis: age, sex, BMI, stone volume, mean stone density, stone level, skin-to-stone distance, presence of rim sign.

Table 7.5 Multivariate analysis of prognostic factors for successful ESWL treatment (i.e. stone free at 3 month after one section of ESWL)

Stone Characteristics	AOR (95% CI)	P value
Stone volume (SV ≤ 0.2 cc vs. SV > 0.2 cc)	4.297 (1.422, 12.985)	0.01
Mean stone density (MSD ≤ 593 HUs vs. MSD > 593 HUs)	3.497 (1.073, 11.391)	0.038
Skin-to-stone distance (SSD ≤ 9.2 cm vs. SSD > 9.2 cm)	3.388 (1.154, 9.941)	0.026

Table 7.6 Association between the number of predictive factors and stone-free rate

Scoring system for the prediction of treatment outcome of ESWL for upper ureteric stones

Score one point if the upper ureteric stone has the following characteristics.

- Stone volume ≤ 0.2 cc
- Mean stone density (MSD) ≤ 593 HUs
- Skin-to-stone distance (SSD) ≤ 9.2 cm

Score	Stone-free rate	P value
0	17.9% (5/28)	< 0.001
1	48.4% (15/31)	
2	73.3% (22/30)	
3	100% (5/5)	

Table 7.7 Comparison of the study designs and guidelines of the study of Kanao et al.[119], the study of Kacker et al.[130], and our study

	Kanao et al.[119]	Kacker et al. [130]	Our study
Study design	Prospective	Retrospective	Prospective
Subject number	507	325	94
Stone site	Renal and ureteric	Renal and ureteric	Upper ureteric only
Nature of predictor variables	Based on plain radiography or intravenous urography	NCCT	NCCT
Basic statistical methods	Multivariate analysis with a logistic regression model	Assessed by ROC curve of pre-selected parameters and	Multivariate analysis with a logistic regression model
Final predictors of treatment success	Stone length, site, and number	Average stone attenuation	Stone volume, mean stone density, and skin-to-stone distance
Practical guidelines	Nomogram table	Simple guidelines for stones 6-10 mm in size	A 3-point scoring system

Figure 7.1

a) Definition of skin-to-stone distance (white arrow) in this study;

b) Definition of skin-to-stone distance; the mean of three measurements taken at 0°, 45°, and 90°, as suggested by Pareek et al.[121]

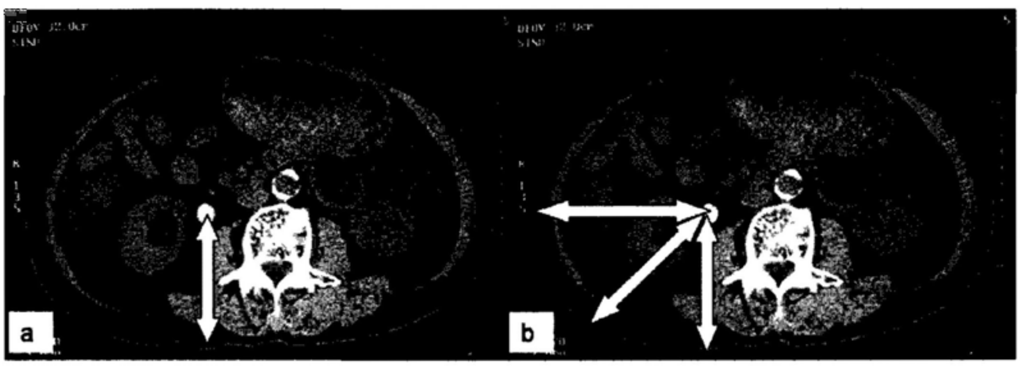


Figure 7.2 Scatter plot of stone volume and mean stone density as measured by NCCT for individual ureteric stones.

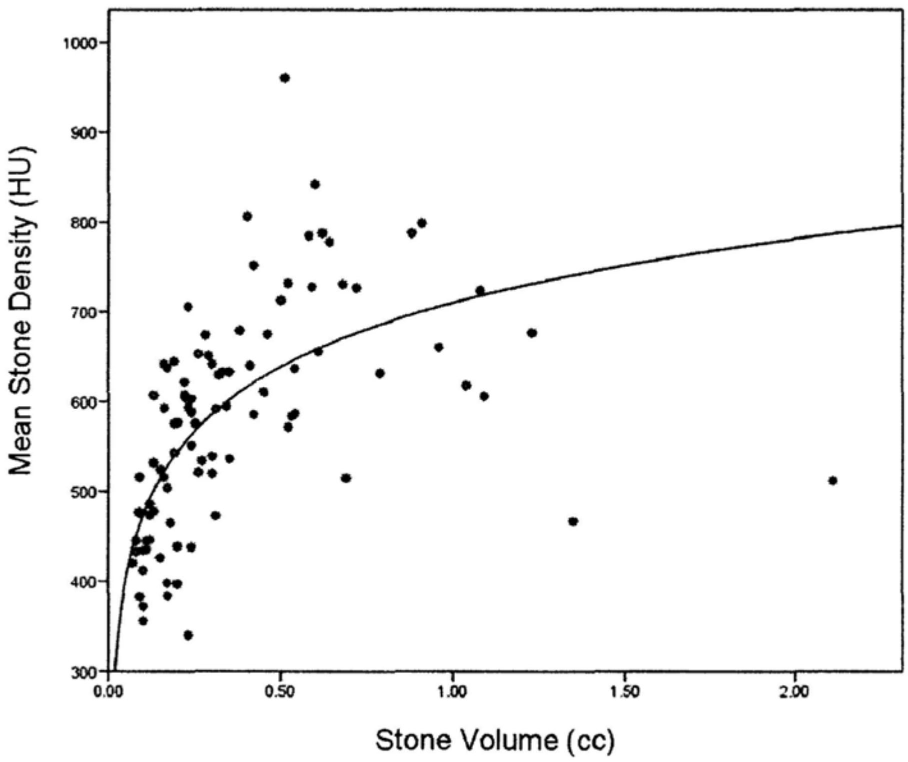
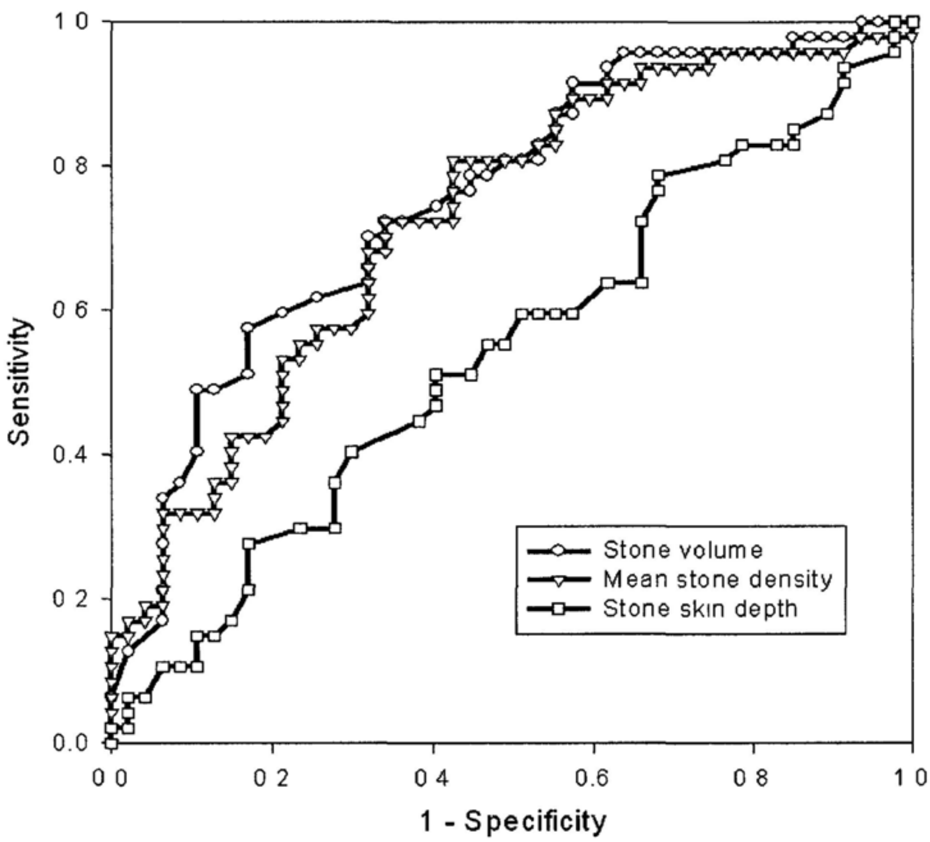


Figure 7.3 ROC curves of stone volume, mean stone density, and skin-to-stone distance for the prediction of stone-free status. (a) All three graphs together; (b) Stone volume alone; (c) Mean stone density alone; (d) Skin-to-stone distance alone.

(a) All three graphs together



The area-under-curve for the three parameters:

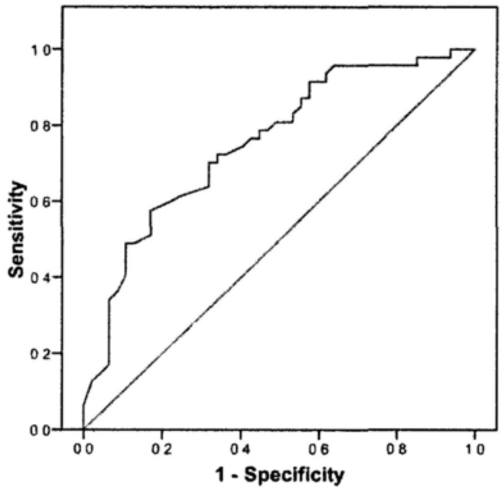
For stone volume (SV) = 0.755

For mean stone density (MSD) = 0.728

For stone-skin-depth (SSD) = 0.544

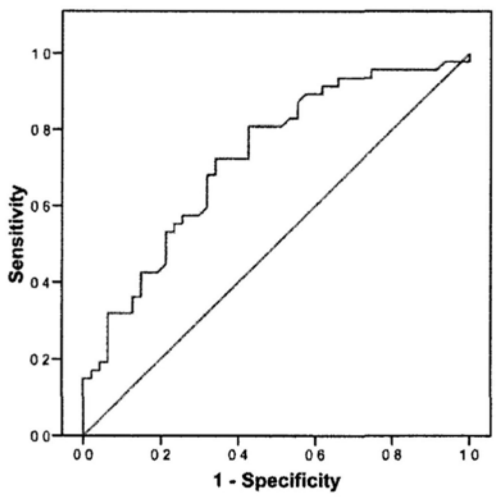
(b) Stone volume

Area-under-curve = 0.755



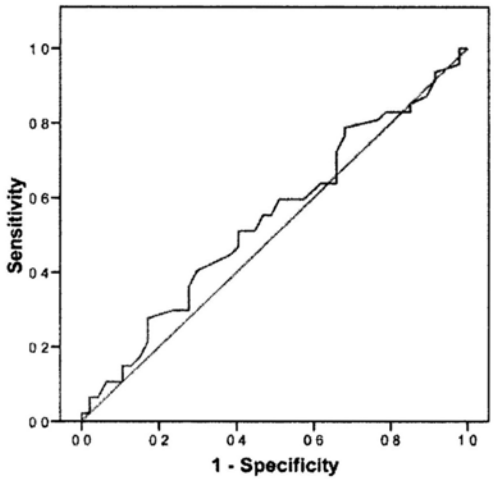
(c) Mean stone density

Area-under-curve = 0.728



(d) Skin-to-stone distance

Area-under-curve = 0.544



Chapter 8

The Applicability of Caliceal Pelvic Height among Different Lithotriptors

Abstract

Objective

To assess the applicability of caliceal pelvic height in the prediction of stone clearance in patients treated with three different lithotriptors within one center.

Materials and Methods

Four hundred and seventy adult patients with solitary, radio-opaque, lower caliceal stones 6-10 mm in size who received primary ESWL between January 1992 and June 2002 were identified. They had been treated with one of three lithotriptors, the Wolf Piezolith 2300, Dornier MPL 9000, or Dornier Compact Delta. Pretreatment intravenous urograms were reviewed and caliceal pelvic height, the vertical distance from the lowermost point of the calyx to the highest point of the lower lip of pelvis, was measured. The primary endpoint was the stone-free rate (SFR) after three months. The adjusted odds ratios (AORs) of different potential predictor variables for the overall result and individual machines were estimated using multiple logistic regression.

Results

In the overall analysis, stone size and machine type were the only predictors associated with stone clearance. The clearance rate was better for smaller stones, and the MPL 9000 appeared to have the best performance, followed by the Piezolith 2300. However, after patients were stratified into different machine subgroups, caliceal pelvic height became a significant predictor of the SFR for the Piezolith 2300 (AOR = 0.960; 95% CI 0.925-0.960; $p = 0.031$) but not the other two machines.

Conclusion

Caliceal pelvic height was useful in the prediction of lower caliceal stone clearance only for the Piezolith 2300. Therefore, the usefulness of one anatomical factor assessed by treatment using one lithotriptor may not be extrapolated to other machines.

I Introduction

Lower caliceal stones are known to have a lower stone-free rate (SFR) after ESWL compared to stones in other sites in the kidney, although individual patients can have excellent clearance rates. One proposed reason is the anatomical configuration of the lower caliceal collecting system, which hinders the passage of stone fragments. [133] However, despite vigorous efforts to identify possible anatomical factors for the prediction of stone clearance, no clear consensus has been reached regarding the utility of these measurements. (Figure 8.1) (Table 8.1) [81, 99-102, 134-140] This may be due in part to differences in the definition of each factor and to inter-observer variation. [141] However, one aspect not previously studied is the effect caused by different types of shock wave generators. The role of one reproducible anatomical factor, caliceal pelvic height (CPH), had been assessed for its relation with the stone clearance rate for lower caliceal stones in three different lithotriptors used within one center.

II Materials and Methods

Four hundred and seventy patients with lower caliceal stones who were treated in our center between January 1992 and June 2002 were included in this study. The inclusion criteria were as follows.

- Adult patients (age $\geq$ 18 years old)
- Patients with normal renal anatomy (those with a horseshoe kidney, duplex kidney, or other such condition were excluded)
- Radio-opaque stone
- maximum diameter 6-10 mm
- ESWL as the primary treatment, including pretreatment stenting or the stone pushed back from the ureter
- Follow-up information available for three months, or until stone-free status was achieved

Three lithotriptors were used in our center during this period: the Wolf Piezolith 2300 (Richard Wolf, Germany) (245 patients), Dornier MPL 9000 (Dornier MedTech, Germany) (105 patients), and Dornier Compact Delta (Dornier MedTech, Germany) (120 patients). The specifications of the three machines are listed in Table 8.2. [16, 17] From 1989 to 1992, all patients referred to our center were treated by the Piezolith 2300. The MPL 9000 was available via a mobile service from 1992. From 1992 until 1999, all local patients were treated by the Piezolith 2300 and patients in other referral areas were treated by the MPL 9000 by the mobile service. In 1999, the Compact Delta was installed to replace the other two machines and all patients were then treated by this machine. During this study period, all of the treatments were delivered by the same team of staff (radiographers) under the supervision of the same consultants. In the study center, all of the patient treatment records and follow-up information were recorded prospectively from 1987 in a computer database, which formed the basis for this review.

All patients who suffered from renal stones had an intravenous urogram for the pretreatment workup. This pretreatment intravenous urogram was reviewed and the CPH of each patient was measured by one urologist, who was blinded for the treatment outcome. CPH was defined as the vertical distance from the lowermost point of the calyx to the highest point of the lower lip of pelvis. (Figure 8.2) [101] The stone-free rate (SFR) after three months was the primary endpoint. It was defined as the absence of radiological evidence of stones on plain radiography at three months or earlier after initial ESWL.

All analysis was performed by SPSS 11.5 for Windows. The crude and adjusted odds ratios (AORs) and the 95% confidence intervals (CIs) of stone-free status after three months for the overall result and individual machines were estimated using simple and multiple logistic regression. Potential predictor variables included stone side, stone size, CPH, presence of a ureteral stent, and type of machine used (for the overall analysis). Stone size was entered as a continuous variable. For the evaluation of the effect of machine used on the overall result, indicator variables were created for the MPL 9000 and Piezolith 2300 (the Compact Delta was used as the reference category). Backwards stepwise selection was used to select the final multivariate logistic regression models, and variables significant at $p < 0.10$ were retained in the final model.

III Results

The stone characteristics for the overall result and individual machines are listed in Table 8.3. More than half of our patients were treated by the Piezolith 2300. The patient characteristics of the three machine subgroups were comparable.

Table 8.4 presents the range, mean, median, and standard deviation of the CPHs for the overall population and each machine subgroup. Except one outliner with CPH = 57mm, otherwise CPH for all the patients were normally distributed. (Figure 8.3) The numbers of patients with a CPH less than 15 mm and greater than or equal to15 mm are also listed. The use of a cutoff point of 15 mm follows the original recommendation of Tuckey et al. [101] In this study, among patients with a CPH < 15 mm, stone clearance was 92%, whereas among those with a CPH ≥ 15 mm, stone clearance was only 52% ($p < 0.05$). However, there was no significant difference (all p values were greater than 0.05) between patients with a CPH < 15 mm or ≥ 15 mm in either the overall or individual machine results. (Table 8.5)

The crude and adjusted odds ratios for being stone free after three months estimated using simple and multiple logistic regression are given in Table 8.6. Only stone size and type of machine were factors associated with a significantly higher chance of being stone free in the multivariate analysis. The MPL 9000 appeared to have the best performance. Patients treated with the MPL 9000 or Piezolith 2300 had a 2.99 (95% CI 1.711, 5.217) and 1.787 (95% CI 2.859) times greater AOR for being stone free than those treated with the Compact Delta, respectively. CPH was not a significant predictor of the SFR after three months in the overall analysis.

To assess the applicability of CPH in predicting the treatment outcomes of individual machines, patients were stratified according to the type of machine used. The subgroup analysis showed that CPH was a predictor of the SFR for the Piezolith 2300 (AOR = 0.960; 95% CI 0.925-0.960; $p = 0.031$). For the other two machines, CPH was not a significant predictor of the SFR.

IV Discussion

Since the innovative proposal of the role of lower pole collecting system anatomy in stone clearance by Sampaio and Aragao, [133] numerous anatomical factors have been assessed. However, more than a decade later, no clear consensus has emerged as to the predictive value or superiority of any of these factors. The main findings in the literature are summarized in Table 8.1, and demonstrate how diverse are the views about the significance of lower caliceal anatomy. A number of reasons have been proposed to account for these differences, including differences in definition, especially regarding the angle of the infundibulum relative to the renal pelvis. A number of ways to measure this have been described: infundibulopelvic angle, [99] lower infundibulopelvic angle, [142] and the angle between the infundibular axis and ureteral or ureteropelvic axis. [100] These various methods have resulted in confusion in the interpretation of results. Knoll et al. found significant inter-observer variation in these complex measurements. [141] Combined with the variation brought about by the effect of the imaging quality, the accuracy of these anatomical measurements is questionable. Simpler anatomical parameters have been suggested to overcome this inconsistency, such as the CPH [101] and infundibular length-to-width ratio. [137] However, the argument continues. Wherein lies the problem?

Lithotriptors are different. Each machine has different treatment efficacy (as measured by the SFR), which is also dependent on treatment protocols and operator experience. Thus, the impact of the effect of the different lithotriptors used by different investigators in these studies may have been underestimated. Most investigators report their experience with a single lithotriptor. For those reports involving more than one lithotriptor, only the overall results have been presented. [102, 136] Therefore, we decided to examine the impact of lower pole anatomy on the SFR for lower caliceal stones treated with three different lithotriptors by the same team of staff, in the hope that this would provide some insight into the impact of lithotriptor type on the usefulness of these anatomical factors.

Only stones 6-10 mm in size were selected for analysis, as these stones are ideal for a single session of ESWL, with reasonable SFRs. In a previous report from our center, infundibulopelvic angle was suggested as an important predictive factor for stone clearance for stones 11-20 mm in size. [136] However, as discussed, measurement of the angle is not simple and lacks consistency. Therefore, we decided to measure CPH, as it is simpler to measure, and the initial results of the predictive value of CPH were quite promising, at least during our study period. [101,139] All measurements were made by the same urologist, who was initially blinded to the treatment outcomes to decrease bias and inter-observer variation. During the selected study period, all of the treatments and follow-up were carried out by the same team, which should have minimized the variation in treatment policy and outcome assessment.

In the overall analysis of the results, only lithotriptor type and stone size were found to be significant predictor factors for stone clearance. CPH was not a significant factor. However, after the patients were stratified into different machine groups, CPH became a predictor for stone clearance for the Piezolith 2300 but not the other two machines. These results were consistent with the hypothesis that there was a difference in the applicability of CPH among the different lithotriptors within the same center. Although other lower pole anatomical parameters were not included in the analysis, it was believed that CPH is a good representative factor to test the postulation regarding the interaction between anatomical factors and the type of lithotriptor used in lower pole stone clearance. The results of this study may help to explain the controversy in the literature about the usefulness of different lower pole anatomical factors.

Our findings, however, remain unexplained. They could be related to the efficacy of stone fragmentation of the lithotriptor used and the type of stone fragment produced. Chaussy et al. reported that the types of stone fragments produced by different lithotriptors were different. [143] Finer particles may more easily be passed than larger ones. However, the quality of the imaging and the retrospective nature of this study made it difficult to assess with accuracy the size of the fragments produced. Further studies of the type of stone fragmentation in both stone-free and non-stone-free patients after ESWL may help to address this issue.

This study could be criticized for the power of the subgroup analysis. However, in the literature, the majority of reports concerning this aspect involve fewer than 100 patients (Table 8.1). In this study, even the smaller subgroup, the MPL 9000 group, contained 105 patients. Therefore, it is believed that the subgroup analysis provides reasonable evidence of the assessment of CPH for each of the machine. Although the retrospective nature and long period of this study were potential drawbacks, it would be practically difficult to recruit the same sample size prospectively within a shorter duration in a single center. The non-randomized allocation of patients to different lithotriptors may also be criticized for introducing potential bias. However, it is not easy, if not impossible, to perform a single-center randomized trial with three lithotriptors for the same type of comparison. In the study center, the assignment of machines was based on the availability of machines and sources of referral during different time periods. There should be no selection bias with respect to anatomical or stone parameters.

Also, the use of plain radiography could have resulted in overestimation of the SFR, compared with the use of non-contrast computerized tomography (NCCT). During the study period (1992-2002), NCCT was not a standard practice in our center, and we had to rely on plain radiography for the assessment of treatment outcome. This is also true for most of the studies in the literature on lower caliceal anatomy. (Table 8.1) Because of the potential limitation in detecting fine fragments, the SFRs for machines with better fragmentation rates may have been overestimated, and this might have affected the interpretation of our results. However, the results still provide some idea of the relative efficacy of different lithotriptors.

Besides considering lower pole anatomical factors, is there any other method to predict lower caliceal stone clearance? Poulakis et al. conducted an excellent study in which they assessed the effect of various factors on lower pole stone clearance. [139] Univariate analysis showed that the pattern of dynamic urinary transport was the most influential predictor of stone clearance. However, this method requires the use of a digital fluoroscopic system during intravenous urography to record the dynamic flow of contrast. In this relatively complex system, the training time and possible inter-observer variation are concerns. In addition, the degree of radiation exposure is higher because of continuous fluoroscopic screening. Therefore, the system is still not widely applied in clinical practice. In summary, a reliable clinically applicable method for predicting lower caliceal stone clearance is still lacking.

The overall SFR after three months in this study was just 45.3%, a rate that is comparable to that of other studies [102, 137, 142] In order that ESWL may remain a competitive alternative treatment to endoscopic procedures, both flexible ureteroscopy and percutaneous surgery, optimum case selection is vital. The Lower Pole I Study Group proposed percutaneous surgery as the treatment of choice for stones larger than 10 mm. [81] There are also several non-randomized studies regarding the use of flexible ureteroscopy for lower caliceal stones with reported SFRs of more than 75%. [144, 145] Thus, failure to further improve the lower pole caliceal stone clearance rates by ESWL will result in endoscopic procedures becoming the treatment of choice for this group of patients if stone-free status, rather than relief of symptoms, is the goal.

V Conclusion

Despite more than a decade of study, controversy remains concerning the predictive value of lower pole caliceal anatomical parameters for stone clearance. In our single-center experience, CPH was predictive of stone clearance among patients treated with the Piezolith 2300 lithotriptor but not among those treated with the other two lithotriptors used in our department. This supports the postulation that the applicability of lower pole anatomical parameters is machine dependent. Further studies to identify better predictive factors for lower caliceal stone clearance to facilitate better case selection are important to improve the treatment outcome of ESWL.

Table 8.1 Summary of the review of the results of key studies of the effect of lower caliceal anatomy on stone clearance after ESWL

("Yes" indicates the parameter was shown to be a significant predictor of stone clearance; "No" indicates the parameter was not shown to be a predictor of stone clearance.)

Author	Machine	Patient no.	Method to assess stone clearance*	Angle**	Infundi-bular width	Infundi-bular length	L/W% ***	CPH ****	Complex calice
Sampaio et al., 1997 [99]	Lithostar plus	74	X-ray	Yes	-	-	-	-	-
Sabnis et al., 1997 [134]	Sonolith 3000	133	X-ray or US	Yes	Yes	-	-	-	Yes
Elbahnasy et al., 1998 [142]	Dornier HM3	21	X-ray	Yes	Yes	Yes	-	-	-
Lojanapiwat et al., 1999 [135]	Storz Modulith SL-20	50	X-ray	Yes	-	-	-	-	-
Keeley et al., 1999 [136]	Dornier MPL 9000, Wolf Piezolith 2300	116	X-ray	Yes	No	No	-	-	No
Gupta et al., 2000 [100]	? Dornier HM3	90	X-ray	Yes	Yes	No	-	-	No
Tuckey et al., 2000 [101]	Dornier MFL 5000	62	X-ray	No	Yes	No	-	Yes	No
Madbouly et al., 2001 [102]	Toshiba Endolith, Dornier MFL 5000, Dornier Lithotriptor S	108	CT +/- US	No	No	No	-	-	*****
Lower Pole 1, 2001 [81]	8 different machines	64	X-ray	No	No	No	-	-	-
Sumino et al., 2002 [137]	Piezolith 2500	63	X-ray	No	Yes	No	Yes	No	-
Sorensen et al., 2002 [138]	Doli 50	246	X-ray	No	No	No	-	No	-
Poulakis et al., 2003 [139]	Piezolith 2500	680	X-ray	Yes	No	No	-	Yes	No
Yan et al., 2004 [140]	Dornier Compact	42	X-ray or US	No	Yes	Yes	Yes	-	-

*X-ray – includes plain X-ray, nephrotomogram, or intravenous urogram; US – ultrasound image; CT – computerized tomogram.
**Angle – Infundibulopelvic angle.
***L/W ratio – Length-to-width/diameter ratio or lower pole ratio.
****CPH – Caliceal pelvic height.
*****Renal morphology (perfect, obstructed, or pyelonephritic) was the only factor that significantly affected the stone-free rate.

Table 8.2 Specifications of the three lithotriptors

	Wolf Piezolith 2300	**Dornier MPL 9000**	**Dornier Compact Delta**
Generator source	Piezoelectric	Electrohydraulic	Electromagnetic
Focusing method	Spherical dish	Ellipsoid reflector	Acoustic lens
Aperture (cm)	30	21	14
Focal distance (cm)	10-12	14	15
Peak pressure at focal point (bar)	1200	1300 or 750 (by PVDF measurement)	210-556 (by PVDF measurement)
Focal zone (W x L, mm)	2.5 x 30	3 x 20	7.7 x 81
Coupling system	Limited water bath	Water cushion	Water cushion
Imaging system	Co-axial ultrasound	X-ray and ultrasound	X-ray and ultrasound

Table 8.3 Patient and stone characteristics of the overall result and each machine group

Parameters	**Overall**	**Wolf Piezolith 2300**	**Dornier MPL 9000**	**Dornier Compact Delta**
Patient number	470	245	105	120
Mean age (range)	51 (20-86)	51.5 (22.7-83)	50.3 (22-81)	50.9 (20-86)
Stone side:				
Right	287	146	65	76
Left	183	99	40	44
Stone size				
Mean	8.03	7.90	8.20	8.13
Standard deviation	1.46	1.46	1.43	1.50
Presence of ureteral stent	71	21	26	24

Table 8.4 Caliceal pelvic height of the overall result and each machine group

	Overall	**Wolf Piezolith 2300**	**Dornier MPL 9000**	**Dornier Compact Delta**
Range (mm)	1-57	1-44	4-44	5-57
Mean (mm)	22.1	21.7	22.1	22.9
Median (mm)	22	22	21	22.5
< 15mm (% patients)	13.8%	13.9%	14.3%	13.3%
≥ 15mm (% patients)	86.2%	86.1%	85.7%	86.7%

Table 8.5 Overall stone-free rates after three months, and with reference to CPH, for the overall result and each machine group

Stone-free rate after three months	**Overall**	**Wolf Piezolith 2300**	**Dornier MPL 9000**	**Dornier Compact Delta**
For all patients	45.3%	46.9%	57.1%	31.7%
For patients with CPH < 15mm	47.7%	58.8%	46.7%	25.0%
For patients with CPH ≥ 15mm	44.9%	45.0%	58.9%	32.7%
P value	0.68	0.14	0.38	0.54

Table 8.6 Crude and adjusted odds ratios (AORs) and 95% confidence intervals (CIs) of the stone-free rates after three months for the overall result and each machine group, estimated by simple and multiple logistic regression

Predictor variables	**Crude odds ratio (95% CI)**	**P value**	**Adjusted odds ratio (AOR) (95% CI)**	**P value**
Stone Side	1.603	0.013	1.457	0.060
Right vs. left	(1.103, 2.330)		(0.984, 2.156)	
Stone Size	0.804	0.001	0.799	0.001
(Maximum diameter measured in mm)	(0.708, 0.913)		(0.701, 0.912)	
Stent - *Yes vs. No*	1.057	0.831	*	
	(0.637, 1.753)			
Machine *(Reference: Dornier Compact Delta)*				
Wolf Piezolith 2300	1.909	0.006	1.787	0.015
	(1.206, 3.022)		(1.117, 2.859)	
Dornier MPL 9000	2.877	< 0.001	2.988	< 0.001
	(1.668, 4.963)		(1.711, 5.217)	
CPH	0.971	0.021	0.975	0.066
(measured in mm)	(0.946, 0.995)		(0.949, 1.002)	

*Dropped from the multivariate model.

Figure 8.1 The measurement of various lower caliceal anatomical factors: (a) infundibular width; (b) infundibular length; and (c) infundibulopelvic angle.

(a) Infundibular width

(b) Infundibular length

(c) Infundibulopelvic angle

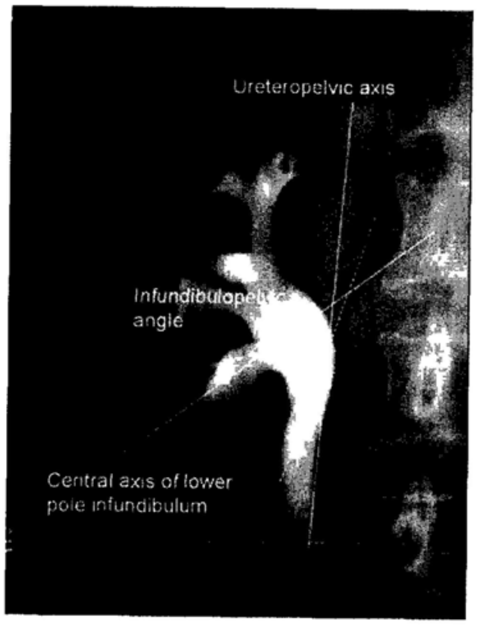


Figure 8.2 The measurement of caliceal pelvic height.

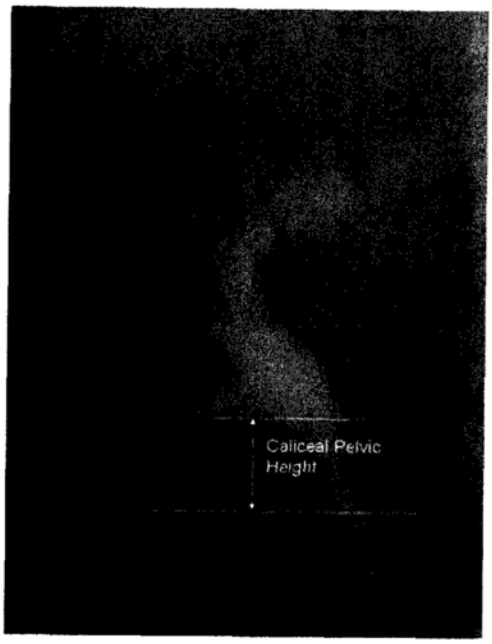
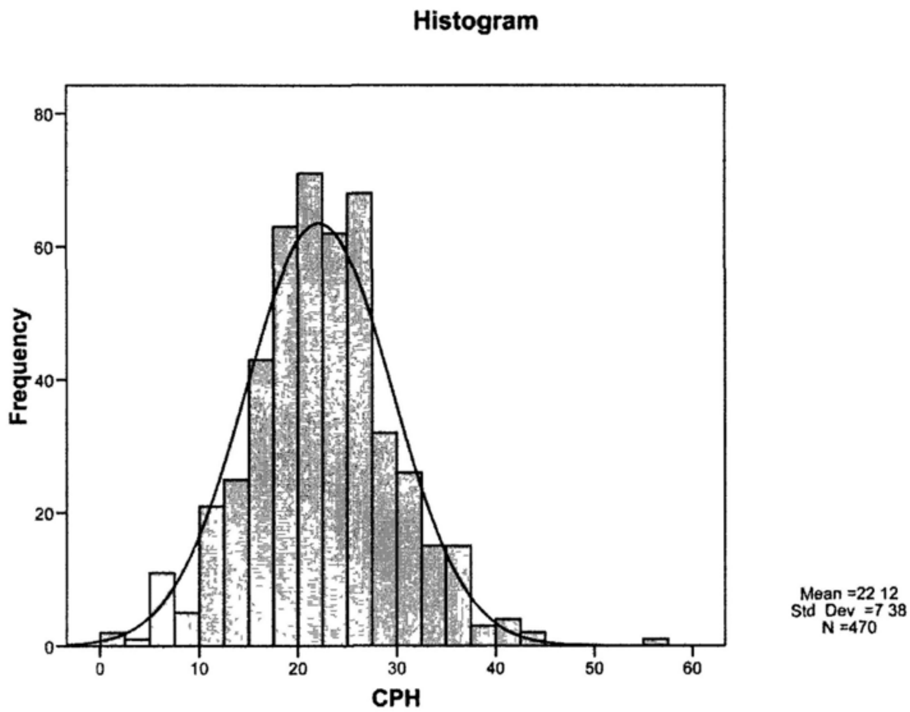


Figure 8.3 Distribution of CPH for the study sample by histogram.



Chapter 9

The Effect of Analgesic Consumption on the Outcome of Shock Wave Lithotripsy

Abstract

Objective

To investigate the effect of additional intravenous analgesia (besides oral analgesic premedication) on the treatment outcome of patients receiving extracorporeal shock wave lithotripsy (ESWL) with the Dornier Compact Delta lithotriptor.

Materials and Methods

Five hundred and twenty adults who received ESWL for the treatment of a solitary urinary stone $\leq$ 10 mm in size were retrospectively reviewed. They received the same analgesic protocol, oral diclofenac 50 mg as premedication, and an additional intravenous bolus of alfentanil if they experienced discomfort during ESWL. After reviewing the analgesic usage, the patients were divided into two groups, Group A – received oral analgesic premedication alone, and Group B – received both oral analgesic premedication and additional intravenous analgesia during ESWL. The treatment outcomes of the two groups were then compared.

Results

There were 306 patients in Group A and 214 patients in Group B. The SFRs at three months for Groups A and B were 38.2% and 44.9%, respectively ($p = 0.100$). The retreatment/auxiliary procedure rates for Groups A and B were 40.8%/12.7% and 35.0%/18.2%, respectively. The additional use of intravenous analgesia improved the effectiveness quotient by 17.7% (from 0.249 [Group A] to 0.293[Group B]).

Conclusion

The additional use of intravenous analgesia during ESWL with the Dornier Compact Delta lithotriptor resulted in the improvement of the effectiveness quotient.

I Introduction

Extracorporeal shock wave lithotripsy (ESWL) therapy has undergone considerable evolution since its introduction in the early 1980s, and one of the main changes is pain management during ESWL. As discussed in Chapter 4, with the original HM-3 lithotriptor (Dornier MedTech, Germany), general anesthesia was almost always necessary. However, for patients treated by the later generation lithotriptors, less potent analgesia and sedation have been used. The avoidance of general anesthesia is undoubtedly beneficial to patients, but there is speculation that less potent analgesic methods may jeopardize treatment outcomes. [103] Therefore, the treatment outcomes of patients with urinary calculi treated with the Dornier Compact Delta lithotriptor (Dornier MedTech, Germany) who received either oral analgesia only or a combination of oral and intravenous analgesia during treatment were reviewed in this study.

II Materials and Methods

A retrospective review of treatment records from April 1999 to March 2002 was performed. Adult patients with solitary renal or ureteric stones less than or equal to 10 mm in size, who had undergone primary ESWL with the Dornier Compact Delta lithotriptor, were identified. Only patients with more than three months' follow-up information available were recruited for analysis.

The Dornier Compact Delta lithotriptor contained an electromagnetic generator with both a fluoroscopic and an ultrasound system for the localization of stones. The aperture size was 380 cm^2 and the focal area was 9 x 90 mm^2, with the focal peak pressure ranging from 16 to 55 MPa. In our unit, all patients treated with ESWL received oral diclofenac 50 mg as premedication about 30 minutes before treatment. Additional analgesia, in the form of intravenous bolus alfentanil, was given to patients during treatment if they experienced pain or discomfort. The dosage of alfentanil given was titrated to the level of patient discomfort with the aim of rendering the patient pain free. Treatment was aimed at a maximum of 4000 shocks per session, or until the stone became difficult to visualize or the patient could not tolerate further treatment.

The following information was retrieved from the prospectively collected computer database for the review.

- Demographic information of the patients – sex, age, and body weight
- Characteristics of the targeted stones – side, site, and size

- Analgesic usage – individuals requiring additional intravenous alfentanil and the dosage given; any adverse effect or extra hospital stay related to analgesic usage was also noted
- Treatment details – total number of shocks and maximum power level used during treatment

Patients were divided into two groups, those who received oral analgesic premedication only (Group A) and those received oral analgesic premedication and intravenous analgesia during ESWL (Group B). The patient, stone, and treatment characteristics and treatment outcomes of the two groups were then compared.

The treatment outcomes assessed were the stone-free rate (SFR) after three months, retreatment rate, and auxiliary procedure rate. These were defined as follows.

- SFR after three months – absence of stone material by plain radiography or ultrasonography done three months or earlier after the initial ESWL treatment session
- Retreatment rate – repeat ESWL for the targeted stone after the initial ESWL
- Auxiliary procedure rate – all interventions, other than repeat ESWL, required for further treatment of the stone or its related complications

The overall treatment outcome was assessed using the effectiveness quotient (EQ), which takes into account each of the above three outcome parameters in the assessment of the efficacy of a lithotriptor. The original formula is as follows [104]:

$$\frac{\%\ \text{stone-free patients}}{100\% + \%\ \text{retreatment} + \%\ \text{auxiliary procedures after ESWL}}$$

However, this original formula does not distinguish between patients who become stone free after ESWL alone and those rendered stone free by retreatment or auxiliary procedures. Therefore, a modified EQ has been suggested, with only the SFR by ESWL alone used, rather than the overall SFR. [146] In this study, we employed the modified EQ, using the SFR at three months after the initial ESWL alone, as doing so would provide a clearer view of the efficacy of the treatment.

Student's *t*-test was used to compare the mean weight and age of patients and the mean number of shocks received by patients. Other parameters, including the patient, stone, and treatment characteristics and treatment outcomes of the two groups were compared using the chi-square test (or Fisher's exact test for group size less than 5).

III Results

During the study period, 530 patients were identified from our prospectively collected computer database. Eight patients were excluded from the study as their follow-up details were missing. Two more patients were excluded because of premature termination of treatment due to medical conditions (one suffered from a vasovagal attack soon after the commencement of treatment and the other developed profound bradycardia during treatment). Neither patient received intravenous analgesia before the termination of the procedure. In total, 520 patients were included for the analysis of whom 306 (58.8%) received oral analgesic premedication alone (Group A) and 214 (41.2%) received oral and additional intravenous analgesia (Group B).

In Group B, the mean dosage of alfentanil was 0.84 mg (range 0.2-2.0 mg). There was no report of any complications related to the analgesics used for the two groups.

The patient and stone characteristics of the two groups are summarized in Table 9.1. The mean age in Group A was 51.9 years (SD = 13.4 years) and that of Group B was 49.9 years (SD = 13.7 years). Patients in Group B were statistically significantly younger ($p < 0.001$, Student's *t*-test) than those in Group A. There was no difference in the sex distribution of the two groups ($p = 0.319$). The other characteristics of the two groups were also similar.

The treatment characteristics of the two groups are given in Table 9.2. There were no statistically significant differences in the number or intensity of shock waves between the two groups.

The overall treatment outcomes are listed in Table 9.3. The SFR after three months, retreatment rate, and auxiliary procedure rate for Group A were 38.2%, 43.7%, and 12.7%, respectively, and those for Group B were 44.9%, 41.1%, and 19.2%, respectively. There was no statistically significant difference among the three outcome parameters between the two groups (the p values for the SFR after three months, retreatment rate, and auxiliary procedure rate were 0.100, 0.181, and 0.085, respectively).

The EQs for Group A and Group B were 0.249 and 0.293, respectively. The additional use of intravenous analgesia improved the EQ by 17.7%.

In Group B, there was no difference in the mean dosage of alfentanil used between patients who became stone free after three months (mean 10.48 mg, standard deviation 5.04 mg) and those who did not (mean 11.40 mg, standard deviation 5.69 mg) ($p = 0.275$).

IV Discussion

The results of this study showed that the additional use of intravenous analgesia in patients receiving ESWL was a safe approach to improve the treatment efficacy, and resulted in a 17.7% improvement in the EQ (from 0.249 [Group-A] to 0.293 [Group-B]). The result supported the hypothesis that better pain control can result in the improvement of the efficacy of ESWL.

Since the introduction of ESWL in clinical practice more than 25 years ago, [56] there have been numerous changes in the machine design. New machines are more user friendly (for patients and clinicians) but have lower efficacy than the original HM-3 lithotriptor. [86, 147] The poorer treatment outcomes that are observed with the latest lithotriptors may be due to various factors, including changes in power source, coupling mechanism, focal zone size, and peak pressure. However, evidence suggests that inadequate analgesia may play a role in the poorer results.

Sorensen et al. performed a retrospective study of the lithotripsy outcomes of 186 patients with a single renal or ureteric stone less than 20 mm in size. [103] The patients received either intravenous sedation (60 patients) or general anesthesia (126 patients) during treatment with the Dornier Doli 50 lithotriptor. The three-month SFR was significantly better among patients treated with general anesthesia (87% for the general anesthesia group and 55% for the intravenous sedation group, $p < 0.01$). The finding of the present study seem to be consistent with that of Sorensen et al. (2005) that better pain control results in better treatment efficacy. However, what is the underlying reason for the improvement in treatment outcome?

Avoidance of patient movement during therapy could be the most important factor, especially given the smaller focal zone of modern lithotriptors compared with the original Dornier HM-3 machine. This proposition is supported by an in vitro study that showed that movement of the patient during treatment and hence movement of the targeted stone by 10 mm reduced the fragmentation rate from 71% to 38%. [148] Increasingly, less potent analgesia is being used during ESWL, and the experience of pain during treatment will inevitably result in movement. This could explain the decrease in efficacy of the latest lithotriptors.

Although the use of general anesthesia for patients undergoing ESWL provides the best pain control and in turn may provide the best treatment results, this must be balanced with the risk to patients, treatment cost, patient turnover rate, and manpower involved. In fact, analgesic protocols tailored for individual patients would be the ideal approach. The pain threshold and analgesic requirement of individual patients are different and depend on many factors. Robert et al. reviewed patients with kidney stones (as opposed to upper ureteric stones) and found that female patients had significantly higher pain scores during ESWL. [149] Salinas et al. found that younger patients required more analgesia during ESWL. [150] The present study also found a significantly higher demand for additional intravenous analgesia during ESWL among younger patients. Therefore, in summarizing the findings of these studies and our study, we suggest that among patients with renal stones, those who are younger and/or female should have a more potent analgesic regimen during ESWL to minimize pain during treatment; this might also improve the treatment outcome. Further studies to identify other contributing factors to assess analgesic demand during ESWL would be helpful in the development of tailor-made analgesic protocols for different patients.

In our current practise, alfentenil is used as analgesics during ESWL. Theorectically, the use of alfentaniel may inhibit ureteric peristalsis, due to its opioid property. However, because of its short acting nature and also only used during ESWL, the effect on post-ESWL stone fragment clearance. Other commonly used analgeics during ESWL include non-steoidal anti-inflammatory drugs (NSAID), such as diclofenac, and tropical agents, such as EMLA cream etc. One of the main potential problems of NSAIDs is the potential effect on platelet function and may increase risk of bleeding. On the other hand, tropical cream is applied locally over the skin and will be free of significant systemic side effects. Unfortunately, the use is less convenience to patients and nursing staff and was less popular in clinical practice.

There were several limitations in this study including its retrospective nature and also small sample size. As a result, some of the information such as patients' body weight, height etc, were missing. Also as the patients need to actively ask for analgesics when pain experienced, this may hinder some patients from requesting for it. Therefore the analgesics consumption may not be actually reflecting the pain experienced by patients. This problem can be overcome by the use of patient-controlled analgesia and also pain assessment by pain scores during ESWL. Finally, despite EQ is recommended as a method for the assessment of the treatment outcomes of ESWL, the intrinsic limitation of the measurment (as discussed in Chapter 10) and the difficulties to demonstrate statistical difference may affect the interpretation of our results. Therefore future prospective studies with better collection of patients' characteristics, body build, stone parameters and treatment parameters, may help to provide more information on the impact of analgesics consumption on treatment outcomes. Also these results may help to identify patient groups that may require more analgesics and allow better design of analgesics regime for our patients.

V Conclusion

Patients who received oral analgesic premedication and additional intravenous analgesia during ESWL with the Dornier Compact Delta lithotriptor seem to have a better treatment outcome (the effectiveness quotient improved by 17.7%) than patients who received oral analgesic premedication alone. Therefore, more liberal use of analgesia during ESWL should be considered as an approach to improve the treatment outcome. However, becauses of the various limitations in this study, further studies maybe needed to confirm our findings.

It was also observed that younger patients required more analgesia during ESWL. Further investigation to identify other factors that could predict the analgesic demand of patients is important for the tailoring of pain treatment protocols for individual patients.

Table 9.1 Patient and stone characteristics of the two groups

	Group A	Group B	p-value
Patient characteristics			
Sex			P=0.319
Male	228 (74.5%)	151 (70.6%)	
Female	78 (25.5%)	63 (29.4%)	
Mean age (years)	51.6	49.9	P<0.001
Mean weight	81.2 kg (250, 81.7% cases available)	80.0 kg (170, 79.4% cases available)	P=0.500
Presence of nephrostomy tube	2 (0.7%)	6 (2.8%)	P=0.070 (by Fisher's exact test)
Presence of ureteric stent	57 (18.6%)	40 (18.7%)	
Stone factors			
Laterality			P=0.398
Right side	116 (37.9%)	89 (41.6%)	
Left side	190 (62.1%)	125 (58.4%)	
Mean size (mm)	7.10	6.98	P=0.517
Stone site			
Upper caliceal stone	11 (3.6%)	15 (7.0%)	
Middle caliceal stone	30 (9.8%)	18 (8.4%)	
Lower caliceal stone	103 (33.7%)	56 (26.2%)	
Renal pelvic stone	28 (9.2%)	17 (7.9%)	
Upper ureteric stone	88 (28.8%)	61 (28.5%)	
Middle ureteric stone	15 (4.9%)	11 (5.1%)	
Lower ureteric stone	31 (10.1%)	36 (16.8%)	

p-value were calculated by Student's t-test and Chi-square test, unless otherwise specified.

Table 9.2 Treatment characteristics of the two groups

	Group A	Group B	P value
Energy Level			
Below level 3 (12.75 kV)	119 (38.9%)	100 (46.7%)	0.075
Above level 4 (14 kV)	187 (61.1%)	114 (53.3%)	
Number of shocks			
Mean	3100	3224	0.068

Table 9.3 Treatment outcomes of the two groups

	Group A	Group B	P value
Stone-free rate at 3 months	38.2%	44.9%	0.100
Retreatment rate	43.7%	41.1%	0.181
Auxiliary procedure rate	12.7%	19.2%	0.085
Effectiveness quotient (EQ)	0.249	0.293	--------

Chapter 10

Comparison of the Outcomes of Different Lithotriptors – The Logistic Regression Approach

Abstract

Objective

To compare the treatment outcomes of extracorporeal shock wave lithotripsy (ESWL) using the Wolf Piezolith 2300 (a piezoelectric lithotriptor), Dornier MPL 9000 (an electrohydraulic lithotriptor), or Dornier Compact Delta (an electromagnetic lithotriptor) from January 1992 to June 2002 in a single center.

Materials and Methods

Three thousand and forty-four patients with solitary, radio-opaque urinary stones ≤ 15 mm in size (3123 stones in total – 1449 treated with the Piezolith 2300, 780 with the MPL 9000, and 894 with the Compact Delta), who received primary ESWL, were identified. Stone-free status was defined as the absence of radiological evidence of stones on plain radiography. Treatment outcomes were assessed by the stone-free rate (SFR) three months after one treatment session, retreatment rate, auxiliary procedure rate, complication rate, and effectiveness quotient (EQ). To better assess the efficacy of individual lithotriptors, multiple logistic regression was performed to control for various factors that could affect treatment outcomes, including lithotriptor type, patient sex and age, history of previous ESWL, stone characteristics (side, site, and size), and the presence of a ureteric stent or nephrostomy tube.

Results

There were significant differences in the stone site distribution and mean stone size among the three groups. The overall EQs for the Piezolith 2300, MPL 9000, and Compact Delta were 0.345, 0.303, and 0.257, respectively. However, using a multiple

logistic regression model, the adjusted odds ratios (AORs) of the SFR after three months for the Piezolith 2300 and MPL 9000 (using the Compact Delta as the reference category) were 1.38 (95% CI 1.15-1.65) and 1.72 (95% CI 1.39-2.11), respectively. Patients treated by the MPL 9000 required significantly less retreatment (AOR = 0.57, 95% CI 0.48-0.69) than those treated by the other two machines. No significant difference in either the auxiliary procedure or complication rate was observed among the three machines.

Conclusion

Multivariate analysis showed that among the three lithotriptors, the Dornier MPL 9000 had the best treatment outcomes in terms of the SFR and retreatment rate.

I Introduction

With the increase in the number of types of lithotriptors available for clinical use, there is a need to develop a standardized method for the comparison of the treatment outcomes of different machines. Treatment cases are not the same, varying in terms of patient characteristics (e.g., age, body build) and stone parameters (e.g., size, site, composition). As the treatment outcome of ESWL is affected by these patient and stone parameters, simple comparison of the overall outcomes of machines is not enough to provide a fair assessment of their performance. A complex mathematical model may be needed to control for all of the potential predictors of treatment outcome. Therefore, a retrospective review of the treatment outcomes, together with logistic regression analysis, was performed for three machines installed in the Scottish Lithotriptor Centre from 1992 to 2002. This study helps to demonstrate the use of logistic regression in the comparison of the performance of different lithotriptors.

II Materials and Methods

Background

Extracorporeal shock wave lithotripsy (ESWL) was introduced into the National Health Service in Scotland in 1987. [151] The therapy was, and continues to be, offered at the Scottish Lithotriptor Centre, Edinburgh, which serves the majority of the population in Scotland. Since the introduction of this treatment modality, extensive experience has been gained with three lithotriptors of different generations: the Wolf Piezolith 2300 (Richard Wolf, Germany), a piezoelectric lithotriptor, the Dornier MPL 9000 (Dornier MedTech, Germany), an electrohydraulic lithotriptor, and the Dornier Compact Delta (Dornier MedTech, Germany), an electromagnetic lithotriptor. The first lithotriptor used was the Piezolith 2300, which was the only lithotriptor capable of providing ESWL without the need for analgesia or anesthesia in the 1980s. Its use was based on the need to facilitate independent travel and outpatient treatment for patients who had to travel a considerable distance for treatment. A mobile lithotriptor service was later introduced in 1992, which used the MPL 9000. The same team was involved in operating the two lithotriptors. In the mobile service, the MPL 9000 was replaced by the Compact Delta in April 1999. At the end of the same year, the Piezolith 2300 was also retired from service. The specifications of the three lithotriptors are listed in Table 10.1 [152,153]

A retrospective review of the treatment outcomes for these three machines from 1992 to 2002 was performed. During the study period, the treatment was delivered by the same team of staff and the treatment protocols for the three machines were similar, except for the premedication. For the Piezolith 2300, no routine pretreatment analgesia was given. If the patient experienced pain, then diclofenac was given orally or by suppository. Patients treated by the other two machines were given diclofenac as premedication. Additional intravenous fentanyl was used if the patients experienced pain during treatment. Ultrasound was the primary imaging modality, which minimized radiation exposure. It was the only means of localization for the Piezolith 2300. Fluoroscopy was also available for the other two lithotriptors, and was particularly useful for difficult cases or ureteral stones. The treatment protocol aimed at a maximum of 4000 shocks per session, or until the stone became difficult to visualize or the patient could not tolerate further treatment. Follow-up radiography, done in either our center or the patient's local hospital, was arranged at four weeks and three months after treatment. The films were then reviewed and if necessary, further treatment decided. The decision to proceed with further ESWL or an auxiliary procedure was based on the patient's initial response to ESWL, the expected result, the risk of the auxiliary procedure, and the patient's choice. The decision process was under the supervision of the same consultants during the study period.

Patient treatment records and follow-up information were all recorded in a computer database prospectively from the introduction of the service. Information was entered by the same team of staff performing the lithotripsy (exclusively by the radiographers from 1992) and thus consistency of standards was maintained. This database formed the basis of this review study.

Study design

The treatment records of patients who received lithotripsy between January 1992 and June 2002 were retrieved from our database for review and analysis.

The inclusion criteria were as follows.

- Adult patients (age ≥ 18 years old)
- Radio-opaque stone
- maximum diameter ≤ 15 mm
- Received ESWL as the primary treatment (stones treated with pretreatment stenting or pushed back from the ureter were also included for analysis)
- Follow-up information available for three months, or until stone-free status was achieved

Patient demographic data, stone characteristics, treatment details, and treatment outcomes were analyzed.

Treatment outcomes assessed were defined as follows.

- Stone free after three months – absence of radiological evidence of stones on plain radiography at three months or earlier after initial ESWL
- Retreatment – repeat ESWL for the index stone
- Auxiliary procedure after ESWL – any intervention, other than repeat ESWL or simple stent removal, required for further treatment of the index stone or related complications

- Complications – emergency hospitalization for the management of symptoms or complications related to the index stone after ESWL

In addition to reporting the overall treatment outcomes, we followed the recommendation of Clayman et al. to stratify the ESWL results according to stone size and site for comparison. [104] In their system, the treatment outcomes are compared among identical groups using the effectiveness quotient (EQ), which is calculated using the following formula:

$$\frac{\text{\% stone-free patients}}{100\% + \text{\% retreatment} + \text{\% auxiliary procedures after ESWL}}.$$

However, this original formula does not distinguish between patients being stone free after ESWL alone and those rendered stone free by auxiliary procedures. Hence, in this analysis, we used the stone-free rate (SFR) three months after one session of ESWL alone to calculate the EQ, which could provide us with a better picture of the efficacy of the lithotriptors. This approach was suggested by Rassweiler et al. [86]

All analysis was performed using SPSS 11.5 for Windows. The chi-square test was used for the comparison of the patient and stone characteristics. Stone size among the three groups was assessed by ANOVA with post hoc adjustment using the Bonferroni approach. The crude and adjusted odds ratios (AORs) for the first four outcomes mentioned and their 95% confidence intervals (CIs) were estimated using simple and multiple logistic regression. [154] Potential predictor variables included patient age and gender, stone nature (first episode or recurrent stone), side, size and site, history of previous ESWL, presence of a percutaneous nephrostomy (PCN) tube or ureteric stent, and type of machine used. Age and stone size were entered as continuous variables. For the evaluation of the effect of machine used, indicator variables were created for the MPL 9000 and Piezolith 2300 (the Compact Delta was used as the reference category). For the evaluation of the effect of stone location by multiple logistic regression, stone location was chosen as the reference category if the location was shown to be about average with respect to the outcome by univariate analysis. Indicator variables dropped from the multivariate models then became part of the reference group. In the univariate analyses for machine and location, all relevant indicator variables were entered simultaneously. All covariates were entered into the multivariate model regardless of their significance level in the univariate model. Backward stepwise selection was used to select the final multivariate logistic regression model, and variables significant at $p < 0.10$ were retained in the final model. Model fit was checked using the Hosmer-Lemeshow goodness-of-fit test statistic, which tests the null hypothesis that the model fits the data well. [155]

III Results

During the study period, 3123 stones (in 3044 patients) were treated: 1449 with the Piezolith 2300, 780 with the MPL 9000, and 894 with the Compact Delta. Patient and stone characteristics are listed in Table 10.2. There were significant differences in the distribution of stones in the kidney and ureter. The numbers of patients with ureteric stones treated with the Piezolith 2300, MPL 9000, and Compact Delta were 211 (14.6%), 288 (36.9%), and 377 (42.2%), respectively. This finding may reflect the fact that only ultrasound localization was available in the Piezolith 2300. The MPL 9000 group had the largest mean stone size compared with the other two groups (both $p<0.001$), and the difference between the latter two groups was not significant ($p = 0.071$).

The treatment characteristics are presented in Table 10.3. The number of shocks given to patients treated with the MPL 9000 was much less than that given to patients treated with either of the other machines. None of the patients treated with the Piezolith 2300 required intravenous analgesia, but it was given to around 40% of those treated with the other two lithotriptors.

The overall treatment outcomes are given in Table 10.4. The overall EQs for the Piezolith 2300, MPL 9000, and Compact Delta were 0.345, 0.303, and 0.257, respectively. The types of auxiliary procedures and complications are listed in Table 10.5. Because of the difference in stone distribution and mean stone size, treatment outcomes (SFR and EQ) were further stratified according to stone size and site, as suggested by Clayman et al., [104] and the results are presented in Table 10.6.

The crude and adjusted odds ratios for being stone free are given in Table 10.7. Multivariate analysis showed that younger age, no history of previous ESWL, absence of a ureteral stent, right-side stone, smaller stone, and middle caliceal, renal pelvic, or lower ureteral stones were factors associated with a significantly higher chance of being stone free. Univariate analysis showed that patients treated with the Piezolith 2300 had the highest chance of being stone free (50.2%), followed by those treated with the MPL 9000 (46.7%) and Compact Delta (40.2%). However, after controlling for the other variables using multiple logistic regression, the MPL 9000 had the best result. Patients treated with the MPL 9000 or Piezolith 2300 had a 1.72 (95% CI 1.39-2.11) and 1.38 (95% CI 1.15-1.65) times greater AOR, respectively, for being stone free than those treated with the Compact Delta. The pair-wise differences among all three machines were statistically significant ($p < .0005$). The results of the Hosmer-Lemeshow goodness-of-fit test indicated that the multivariate model fit the data well ($p = 0.297$).

The crude and adjusted odds ratios for requiring retreatment are given in Table 10.8. In the multivariate model, older age, larger stone size, presence of a ureteral stent, and pelvic, ureteropelvic junction, or upper ureteral stones were all significant predictors of retreatment. Patients treated with the MPL 9000 (AOR = 0.57, 95% CI 0.48-0.69) and those with lower ureteral stones were significantly less likely to require retreatment. The results of the Hosmer-Lemeshow test indicated that the model fit the data very well ($p = 0.615$).

Analysis of the auxiliary procedure and complication rates revealed no significant machine effect for these two outcomes. However, younger patients, males, and those with pelvic or middle ureteric stones were significantly more likely to have complications. Older patients, those with larger stones, those who required PCN or ureteric stenting, and those with stones in the ureteropelvic junction or the upper, middle, or lower ureteric region had a significantly higher chance of having an auxiliary procedure. Patients with stones in the lower caliceal region were significantly less likely to have an auxiliary procedure.

IV Discussion

There are many approaches to compare the performance of different generator sources and machines. In vitro comparison of machines or generators has been done by direct measurement of the physical parameters at the focal area, using either a hydrophone or an electromagnetic probe. [156] Comparison of the degree of fragmentation of artificial stones with that of human stones has also been undertaken. [157, 158] However, these results may not directly reflect the clinical situation. [158] Moreover, the complication and auxiliary procedure rates are also outcomes that need to be addressed, in addition to the stone-free and fragmentation rates. Therefore, clinical studies remain the most informative for practising urologists regarding the assessment of lithotriptors.

There are many types of clinical studies of ESWL. The prospective randomized study is the ideal, but there are few such studies published. [91, 159, 160] The majority of studies have been performed retrospectively. Another factor to be considered is whether the study is a single- or multicenter one. This is important, as the treatment philosophy of each center, including the analgesic/anesthetic protocol, shock wave delivery rate, follow-up protocol, and retreatment threshold, will affect outcomes. [161, 162] The experience of the operating staff performing ESWL is also important. [163] Thus, single-center studies are more likely to provide more conclusive results than are multicenter ones.

This is the first single-center clinical comparison of lithotriptors with three generator sources. Although the study was carried out retrospectively, the information contained in the computer database was collected contemporaneously by the same group of staff. Therefore, the internal consistency of these data is very high, which should minimize the potential bias related to retrospective studies.

For the comparison of treatment outcomes of different lithotriptors, Clayman et al. recommend the stratification of the ESWL results according to stone size and stone site. [104] The SFR at three months, retreatment rate, and auxiliary procedure rate can then be compared among identical groups using the EQ to summarize the outcomes. Initially, we tried to follow this approach in analyzing the results. However, despite the inclusion of over 3000 cases, after stratification, some subgroups had only small numbers of cases (Table 10.6). Also, the large number of EQs (24 categories in our study) can make it difficult to interpret the results and come to a conclusion. Moreover, this stratification system controls only for stone size and site, and does not include other factors, such as the presence of a ureteral stent. Therefore, the EQ may not be the ideal method for the comparison of the treatment outcomes of different lithotriptors, especially when the treatment groups are not similar.

Univariate and multivariate statistical analyses were performed for further analysis of the results. This approach has also been used in other studies. [97, 109, 160] The advantage is that clinical factors other than stone size and site can be controlled for at the same time, and the individual effect of these factors on treatment outcome can be assessed. It is believed that this is a better approach for the comparison of the efficacy of different lithotriptors. Our results showed that the MPL 9000 had the best outcome, based on its higher AOR for the SFR at three months and significantly lower AOR for retreatment. The Piezolith 2300 had a better SFR than had the Compact Delta, but the retreatment rates were similar for these two machines. The auxiliary procedure and complication rates were similar among all three machines.

The exact reason for the better treatment outcome of the MPL 9000 is not known. It is believed that the generator source is only one of the factors that affect lithotriptor performance. The large size of the focal zone of the Dornier HM-3 (15 x 90 mm) is thought to be an important factor for its excellent performance. [152, 157] However, the large size of the focal zone does not explain the result of this study, as the Compact Delta has the largest focal zone (7.7 x 81 mm) among the three lithotriptors. Similarly, peak pressure alone cannot explain the superiority of the MPL 9000. Based on an in vitro comparison of seven lithotriptors, Teichman et al. concluded that peak pressure and focal zone volume were not correlated with the fragmentation outcome. [157] In fact, the effectiveness of the coupling mechanism and accuracy of the imaging technique are also important. Whereas the Piezolith 2300 uses a limited water bath for coupling, the other two machines use a water cushion, which can result in a 15-25% loss of shock wave energy as compared to the water bath. [86] In addition, the coaxial ultrasound localization of the Piezolith 2300 and MPL 9000 theoretically provides more accurate targeting than does the lateral ultrasound localization of the Compact Delta. [164] The use of fluoroscopy in the localization and monitoring of target stones can improve the outcome for ureteral stones. Given the abovementioned findings, we believe that the success of a lithotriptor relies on the whole effect produced by the different parts of the machine.

This study may be criticized for the long study period of ten years, which could result in a change in treatment policy. However, in our center, because of the large population served and limited operating sessions for stone patients with a solitary stone less than 15 mm in size, ESWL remained the first-line treatment for stone management during this period. Because the treatment was supervised by the same consultants, the policy for retreatment and auxiliary procedures did not change over these years.

It is understood that the use of plain radiography (including tomography) can result in overestimation of the SFR compared with the use of non-contrast computerized tomography (NCCT). However, the latter technique was not a standard practice in the first years of our center; rather, plain radiography was routinely used for the assessment of stone fragmentation and clearance of radio-opaque stones. It continues to be used for follow-up assessment, as NCCT is still not readily available. Another important concern about the use of routine NCCT for follow-up is the radiation dose related to this imaging modality, which is much higher than that of plain radiography. This is especially important if repeated imaging for follow-up is needed.

Another limitation of this study is the lack of information about the stone composition, which also affects the treatment outcome. However, only patients with untreated radio-opaque stones were included, of which the majority would be calcium-containing stones. However, as the patient number of each treatment group was large (the smallest was 780 for MPL 9000), it is hoped that the effect of different stone composition averaged out among the groups.

V Conclusion

A single-center retrospective review was conducted of the treatment outcomes of three lithotriptors of different generator design, the Wolf Piezolith 2300 (a piezoelectric lithotriptor), Dornier MPL 9000 (an electrohydraulic lithotriptor), and Dornier Compact Delta (an electromagnetic lithotriptor). Multiple logistic regression analysis revealed that the Dornier MPL 9000 had better stone-free and retreatment rates than had the other two machines. The feasibility of using logistic regression for the comparison of the treatment outcomes of different lithotriptors and its advantage in controlling various patient and stone parameters at the same time was demonstrated. This comparison method can provide a reference in the future comparison of the performance of different lithotriptors.

Table 10.1 Specifications of the three lithotriptors

	Wolf Piezolith 2300	**Dornier MPL 9000**	**Dornier Compact Delta**
Generator source	Piezoelectric	Electrohydraulic	Electromagnetic
Focusing method	Spherical dish	Ellipsoid reflector	Acoustic lens
Aperture (cm)	30	21	14
Focal distance (cm)	10-12	14	15
Peak pressure at focal point (bar)	1200	1300 or 750 (by PVDF measurement)	210-556 (by PVDF measurement)
Focal zone (W x L, mm)	2.5 x 30	3 x 20	7.7 x 81
Coupling system	Limited water bath	Water cushion	Water cushion
Imaging system	Co-axial ultrasound	X-ray and ultrasound	X-ray and ultrasound
Period of service	1989-1999	1992-1999	1999-2003

Table 10.2 Patient and stone characteristics of the three lithotriptor groups

	Wolf Piezolith 2300	Dornier MPL 9000	Dornier Compact Delta	
Number of patients	1449	780	894	
Male	1031 (71.2%)	564 (72.3%)	643 (71.9%)	
Female	418 (28.8%)	216 (27.7%)	251 (28.1%)	
Mean age (years)	50.31	50.08	50.15	
Stone nature				P < 0.001
First stone	1307 (90.2%)	674 (86.4%)	751 (84.0%)	
Recurrent stone	142 (9.80%)	106 (13.6%)	143 (16.0%)	
Stone side				insignificant
Right: Left	623 (43.0%) : 826 (57.0%)	321 (41.2%) : 459 (58.8%)	368 (41.2%) : 526 (58.8%)	
Stone site				
Kidney	1238 (85.4%)	492 (63.1%)	517 (57.8%)	P < 0.001
Upper caliceal	137 (9.5%)	34 (4.4%)	38 (4.3%)	
Middle caliceal	204 (14.1%)	54 (6.9%	61 (6.8%)	
Lower caliceal	604 (41.7%)	240 (30.8%)	267 (29.9%)	
Renal pelvic	219 (15.1%)	106 (13.6%)	112 (12.5%)	
Ureteropelvic junction	74 (5.1%)	58 (7.4%)	39 (4.4%)	
Ureter	211 (14.6%)	288 (36.9%)	377 (42.2%)	P < 0.001
Upper	77 (5.3%)	272 (34.9%)	222 (24.8%)	
Middle	0 (0%)	0 (0%)	38 (4.3%)	
Lower	134 (9.2%)	16 (2.1%)	117 (13.1%)	
Stone size				
Mean stone size (mm)	7.76	9.26*	8.06	* P< 0.001 compared to the other two groups
Size subgroups				
1-5 mm	418 (28.8%)	114 (14.6%)	186 (20.8%)	
6-10 mm	745 (51.4%)	389 (49.9%)	541 (60.5%)	
11-15 mm	286 (19.7%)	277 (35.5%)	167 (18.7%)	

Table 10.3 Treatment characteristics of the three lithotriptor groups

Number of patients	Wolf Piezolith 2300	Dornier MPL 9000	Dornier Compact Delta	p- value
History of previous ESWL	88 (6.1%)	40 (5.1%)	96 (10.7%)	P < 0.001
Ureteric stent in situ	144 (9.9%)	235 (30.1%)	197 (22.0%)	P < 0.001
Percutaneous nephrostomy tube in situ	16 (1.1%)	17 (2.2%)	20 (2.2%)	P = 0.058
Required intravenous analgesia	0 (0%)	344 (44.1%)	369 (41.3%)	P < 0.001
Mean number of shocks given per session (range)	3052.57 (450-4000)	1437.54 (425-4000)	3257.45 (350-4000)	--

Table 10.4 Overall treatment outcomes of the three lithotriptor groups

	Wolf Piezolith 2300	**Dornier MPL 9000**	**Dornier Compact Delta**	**p-value**
Initial stone fragmentation rate	86.1%	81.7%	78.7%	$P < 0.001$
Stone-free rate at three months	50.2%	46.7%	40.2%	$P = 0.157$
Retreatment rate	37.7%	36.0%	40.5%	$P = 0.157$
Auxiliary procedure rate	7.9%	17.9%	15.7%	$P < 0.001$
Complication rate	3.0%	4.2%	3.9%	$P = 0.289$
Overall EQ	0.345	0.303	0.257	--

Table 10.5 Post-ESWL auxiliary procedures and complications of the three lithotriptor groups

	Wolf Piezolith 2300	Dornier MPL 9000	Dornier Compact Delta	p-value
Post-ESWL auxiliary procedure				
Ureteroscopic stone removal	71 (4.9%)	91 (11.7%)	121 (13.5%)	
Percutaneous nephrolithotomy	6 (0.4%)	16 (2.1%)	7 (0.8%)	
Stenting	31 (2.1%)	27 (3.5%)	7 (0.8%)	
Percutaneous nephrostomy tube insertion	4 (0.3%)	-	2 (0.2%)	
Other	3 (0.2%)	6 (0.8%)	3 (0.3%)	
Total	115 (7.9%)	140 (17.9%)	140 (15.7%)	P < 0.001
Complication				
Loin pain/colic required hospital admission	41 (2.83%)	30 (3.85%)	31 (3.47%)	
UTI/sepsis	2 (0.14%)	2 (0.26%)	2 (0.22%)	
Perinephric abscess	-	-	1 (0.11%)	
Other	1 (0.06%)	1 (0.13%)	1 (0.11%)	
Total	44 (3.04%)	33 (4.23%)	35 (3.91%)	P = 0.289

Table 10.6 Subgroup analysis of the stone-free rate after three months (SF3m) and effectiveness quotient (EQ)

Site	Size (mm)	Number of patients/SF3m (%)/EQ								
		Wolf Piezolith 2300			Dornier MPL 9000			Dornier Compact Delta		
Upper caliceal stone	1-5	67	61.2	0.500	6	33.3	0.285	19	52.6	0.454
	6-10	55	50.9	0.364	15	53.3	0.421	13	38.5	0.263
	11-15	15	20.0	0.111	13	30.8	0.182	6	50.0	0.300
Middle caliceal stone	1-5	67	76.1	0.660	14	85.7	0.800	22	54.5	0.414
	6-10	110	44.5	0.318	21	61.9	0.479	36	52.8	0.402
	11-15	27	48.1	0.317	19	47.4	0.311	3	0	0
Lower caliceal stone	1-5	183	61.7	0.511	37	64.9	0.586	57	36.3	0.255
	6-10	320	48.4	0.342	127	55.1	0.366	161	33.5	0.236
	11-15	101	24.8	0.142	76	43.4	0.303	49	24.5	0.146
Renal pelvic stone	1-5	11	63.6	0.500	1	0	0	2	0	0
	6-10	106	46.2	0.803	36	52.8	0.346	61	49.2	0.319
	11-15	102	38.2	0.228	69	24.8	0.145	49	32.7	0.198
Ureteropelvic junction stone	1-5	9	66.7	0.462	3	66.7	0.400	3	100	1
	6-10	41	41.5	0.236	33	39.4	0.241	29	31.0	0.319
	11-15	24	37.5	0.214	22	22.7	0.111	7	28.6	0.198
Upper ureteric stone	1-5	11	36.4	0.500	51	64.7	0.446	39	61.5	0.428
	6-10	52	32.7	0.172	148	47.3	0.281	143	43.3	0.250
	11-15	14	7.1	0.030	73	21.9	0.111	40	25.0	0.123
Middle ureteric stone	1-5	0	-	-	0	-	-	9	66.7	0.500
	6-10	0	-	-	0	-	-	27	44.4	0.273
	11-15	0	-	-	0	-	-	2	100	1
Lower ureteric stone	1-5	70	82.9	0.683	2	100	1	35	57.1	0.369
	6-10	61	68.9	0.494	9	88.9	0.800	71	45.1	0.265
	11-15	3	33.3	0.200	5	80.0	0.667	11	9.1	0.044

Table 10.7 Univariate and multivariate predictors of the stone-free rate after three months

Covariate	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age	0.982 (0.977, 0.989)	< .0005	0.987 (0.982,0.992)	< .0005
Gender				
Female vs. male	0.96 (0.82, 1.12)	0.682	*	
Stone nature				
Recurrent vs. first	0.82 (0.66, 1.02)	0.071	*	
Stone side				
Left vs. right	0.83 (0.72, 0.95)	0.008	0.83 (0.71, 0.96)	0.015
Stone size				
(Maximum diameter measured in mm)	0.85 (0.83, 0.87)	< .0005	0.85 (0.83, 0.87)	< .0005
Previous history of ESWL treatment				
Yes vs. no	0.69 (0.52, 0.91)	0.008	0.58 (0.43, 0.78)	< .0005
Presence of nephrostomy tube				
Yes vs. no	0.75 (0.43, 1.31)	0.316	*	
Presence of stent				
Yes vs. no	0.66 (0.55, 0.80)	< .0005	0.73 (0.60, 0.89)	0.002
Machine				
(Referent: Dornier Compact Delta)				
Wolf Piezolith 2300	1.51 (1.27, 1.78)	< .0005	1.38 (1.15, 1.65)	< .0005
Dornier MPL 9000	1.30 (1.07, 1.58)	0.007	1.72 (1.39, 2.11)	< .0005
Stone site				
(Referent: all other sites)				
Middle caliceal stone	1.48 (1.16, 1.89)	0.002	1.41 (1.10, 1.81)	0.007
Renal pelvic stone	0.80 (0.64, 0.99)	0.044	1.27 (1.01, 1.65)	0.042
Ureteropelvic junction stone	0.74 (0.53, 1.02)	0.067	*	
Upper ureteric stone	0.83 (0.68, 1.01)	0.069	*	
Lower ureteric stone	1.99 (1.52, 2.61)	< .0005	1.79 (1.35, 2.37)	< .0005

*Dropped from the multivariate model.

Table 10.8 Univariate and multivariate predictors of the retreatment rate

Covariate	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age	1.011 (1.005, 1.016)	< .0005	1.005 (1.000, 1.011)	0.051
Gender				
Female vs. male	1.01 (0.86, 1.19)	0.866	*	
Stone nature				
Recurrent vs. first	0.86 (0.69, 1.08)	0.187	*	
Stone side				
Left vs. right	1.12 (0.96, 1.29)	0.145	*	
Stone size				
(Maximum diameter measured in mm)	1.19 (1.16, 1.22)	< .0005	1.19 (1.15,1.22)	< .0005
Previous history of ESWL treatment				
Yes vs. no	0.79 (0.59, 1.05)	0.108	*	
Presence of nephrostomy tube				
Yes vs. no	1.25 (0.72, 2.17)	0.422	*	
Presence of stent				
Yes vs. no	1.60 (1.34, 1.93)	< .0005	1.46 (1.20, 1.78)	< .0005
Machine				
(Referent: Dornier Compact Delta)				
Wolf Piezolith 2300	0.889 (0.749, 1.054)	0.175	*	
Dornier MPL 9000	0.83 (0.68, 1.01)	0.061	0.57 (0.48, 0.69)	< .0005
Stone site				
(Referent: all other sites)				
Renal pelvic stone	1.827 (1.469, 2.272)	< .0005	1.22 (0.97, 1.54)	0.086
Ureteropelvic junction stone	1.814 (1.317, 2.272)	< .0005	1.73 (1.25, 2.41)	0.001
Upper ureteric stone	1.460 (1.196, 1.782)	< .0005	1.52 (1.23, 1.87)	< .0005
Lower ureteric stone	0.521 (0.382, 0.710)	< .0005	0.65 (0.47, 0.89)	0.007

*Dropped from the multivariate model.

Chapter 11

Comparison of the Outcomes of Different Lithotriptors – The Matched-Pair Analysis Approach

Abstract

Objective

To compare the treatment outcome of the Piezolith 3000, a new lithotriptor, with that of an older piezoelectric lithotriptor, the Piezolith 2300, using matched-pair analysis.

Materials and Methods

Patients with solitary, radio-opaque urinary calculi who underwent primary lithotripsy with the Piezolith 3000 and had a three-month follow-up were identified. These patients were matched with patients from our database who were treated between 1992 and 1999 with a Piezolith 2300. The patients were initially matched for gender and side and site of the stone. For stones other than those in the lower calyx or lower ureter, matching was then performed for size using both the maximum and minimum diameter of the index stone. Additional anatomical factors including caliceal pelvic height and vertical level of the lower ureteric stone from the pubic symphysis were also measured. Thereafter, stones within ± 1 mm of the index stone were selected and the one for which the anatomical factors were the best match was chosen. The initial stone fragmentation rates and stone-free rates (SFRs) at three months of the matched pairs were then compared.

Results

Twenty-five matched pairs were found for the period between October 2002 and December 2002. There was no statistical difference in the initial fragmentation rate between the Piezolith 3000 (68%) and Piezolith 2300 (84%) ($p = 0.388$, McNemar's test). The SFRs at three months for the Piezolith 3000 and Piezolith 2300 were 36%

and 48%, respectively, again with no statistical difference ($p = 0.581$, McNemar's test).

Conclusion

Despite significant design changes and technical modifications, the new piezoelectric lithotriptor does not appear to provide a treatment outcome better than that of the older generation machine.

I Introduction

The Piezolith 3000 (Richard Wolf, Germany) is one of the latest models of piezoelectric lithotriptors. Because of the extensive experience in ESWL of staff at the Scottish Lithotriptor Centre, a three-month clinical trial was done at the Centre in 2003. One hundred and twenty-eight patients were treated during the trial period. The results were then compared with those of an earlier generation model, the Piezolith 2300, which had previously been used in the Centre. The aim of this comparison was to determine whether the design changes have resulted in an improvement in treatment outcome. The comparison was done using matched-pair analysis following Portis et al., [165] with some modifications.

II Materials and Methods

The Piezolith 3000 was used in our center for a trial period between October 2002 and December 2002, and 128 patients were treated. The inclusion criteria for our comparative study were as follows.

- Adult patients (age ≥ 18 years old)
- Solitary, radio-opaque stone (excluding upper and mid-ureteric stones)
- No prior percutaneous nephrostomy or stenting
- Receiving primary treatment with the Piezolith 3000
- Follow-up information available for a minimum of three months or until stone-free status is achieved

From these 128 cases, 26 cases were included in this study. These patients were matched against patients with stones treated with a Piezolith 2300, the machine previously used in our institution. A prospectively collected database of treatment characteristics and outcomes was available. We selected patients from the database from January 1992 to March 1999 for whom treatment was given by the same treatment team (radiographers) under the supervision of the same director. There were 3747 stones identified. The same selection criteria for treatment by the Piezolith 3000 were then applied to those treated by the Piezolith 2300, and finally, 1226 cases were selected for matching.

The specifications of the two lithotriptors are listed in Table 11.1. The innovative design of the new machine includes a double-layer piezoelectric shock wave source, which increases the power and working life of the generator. The Piezolith 3000 has a smaller focal zone (3 mm x 15 mm) than that of the Piezolith 2300 (2.5 mm x 30 mm), which results in more precise delivery of shock waves and less tissue trauma. In addition, rather than using a limited water bath, the new machine uses a water cushion as the coupling system, which can be handled more easily. The use of a water cushion also allows the therapy head to be moved horizontally on an angle from +50 to -60 degrees, unlike the Piezolith 2300, in which the shock wave could only come upward from the base of the water basin. This new design allows simple and fast positioning of the therapy head/shock wave towards the targeted area. In addition, the incorporation of a fluoroscopic localization system, in additional to the in-line ultrasound system, enables the new machine to treat stones throughout the urinary tract, especially upper and mid-ureteric stones.

The treatment protocols for the two machines were similar. Patients were treated as day cases, and each treatment was aimed at a maximum of 4000 shocks or until the stone could not be visualized. The main difference was the analgesic protocol. With the Piezolith 2300, no premedication was given. If the patient felt pain during treatment, then a diclofenac suppository was administered. With the Piezolith 3000, oral diclofenac 50 mg was given as pre-medication, and additional analgesia, in the form of an intravenous bolus of alfentanil, was given if necessary to control pain.

The matching procedures are described as follows and summarized in Figure 11.1.

First, patient gender and stone laterality and site were matched. Stone sites were classified as upper, middle, or lower calix, renal pelvis, ureteropelvic junction, and lower ureter (below the sacroiliac joint). As the Piezolith 2300 used only ultrasonography for stone localization, very few upper ureteric and no mid-ureteric stones were treated in situ by this machine. Therefore, these stones were excluded in the analysis. Further matching for stone size and additional anatomical factors for particular stone sites was then performed. For upper caliceal, middle caliceal, renal pelvis, and ureteropelvic junction stones, only stone size was further matched. Exact matching in terms of maximal and minimal diameter was attempted first. If no exact match for size was found, then the size was extended to ± 1mm for both diameters. For example, if there was no exact match available for an index stone 5 x 3 mm in size, then the search for a matching stone was extended to stones in the range of 4-6 mm x 2-4 mm in diameter.

For lower caliceal stones, as caliceal anatomy may affect stone clearance, [142] an additional anatomical factor, caliceal pelvic height (CPH), was taken into consideration in the matching process (Figure 11.2). It was defined as the vertical distance from the lowermost point of the calyx to the highest point of the lower lip of the pelvis. During the matching process, all stones within ± 1mm of both diameters of the index stone were selected, and then all of the X-ray films of the selected stones were reviewed and the CPH measured. The one with the closest CPH was selected as the matched stone.

Similarly, for lower ureteric stones, the position of the stone may affect the chance of stone passage. [166, 167] Stones were matched for this parameter, in addition to stone size, by measuring the vertical distance from the upper border of the pubic symphysis to the lower border of the ureteric stone. This measurement was termed the lower ureteric stone height (LUH), (Figure 11.3) and served as an indicator of the distance of the stone from the vesico-ureteric junction (VUJ). Although it may not be accurate in the assessment of the actual distance of the stone from the VUJ, it provided a reasonable guide for the match as all radiographs were taken using a standard protocol. The subsequent matching steps were similar to those for lower caliceal stones.

In all cases, if more than one suitable match was available, then the final matching was directed by random numbers generated by computer and the stone with the smallest number was selected.

After matching was completed, the treatment outcomes in terms of initial stone fragmentation rate and the SFR at three months were compared using McNemar's test.[168]

III Results

Twenty-six cases treated by the Piezolith 3000 were identified. Successful matching was performed for 25 cases. The only stone that could not be matched was an 18 mm stone located at the ureteropelvic junction.

The study group included 18 males and 7 females. The mean ages of patients treated by the Piezolith 2300 and Piezolith 3000 were 50.40 ± 13.20 and 51.72 ± 16.04, respectively. Ten stones were on the right side and 15 on the left. The distribution of stones was as follows: upper caliceal stone – 1 (4%), middle caliceal stones – 2 (8%), lower caliceal stones – 12 (48%), renal pelvic stones – 4 (16%), ureteropelvic junction stones – 2 (8%), and lower ureteric stones – 4 (16%).

The characteristics of the stones treated by Piezolith 3000 and the matched stones treated by Piezolith 2300 were listed in Table 11.2. The summary of the mean stone sizes of the two groups is listed in Table 11.3. There were 14 cases of exact matches for maximal diameter and 12 cases for minimal diameter. Overall, 10 cases (40%) were an exact match for both diameters.

For lower caliceal stones, the CPHs for the Piezolith 2300 and Piezolith 3000 ranged from 17-31 mm and 18-48 mm, respectively. The mean difference (Piezolith 3000 minus Piezolith 2300) and mean absolute difference (Piezolith 3000 minus Piezolith 2300) were 1.75 mm (range -6 mm to 22 mm) and 3.58 mm (range 1 mm to 22 mm), respectively. For the lower ureteric stones, the LUHs for the Piezolith 2300 and Piezolith 3000 ranged from 39-55 mm and 38-80 mm, respectively. The mean difference (Piezolith 3000 minus Piezolith 2300) and mean absolute difference (Piezolith 3000 minus Piezolith 2300) were -6.25 mm (range -25 mm to 1 mm) and 6.75 mm (range 1 mm to 25 mm), respectively.

Only two patients in the Piezolith 2300 group required analgesia during treatment. In the Piezolith 3000 group, three patients required additional intravenous alfentanil during treatment. Nine patients required the use of fluoroscopy screening for localization during treatment with the Piezolith 3000 (one with a ureteropelvic junction stone; two with lower caliceal stones, two with renal pelvic stones, and all four with lower caliceal stones).

The initial stone fragmentation rate and SFR three months after one session of ESWL for both machines are listed in Table 11.4. The distributions of the matched pairs according to machine and treatment outcome are listed in Table 11.5. There were no statistically significant differences in the initial stone fragmentation rate ($p=0.388$) or SFR at three months between the two machines ($p = 0.581$) using McNemar's test.

IV Discussion

Since the introduction of the HM-3 lithotriptor in the early 1980s, ESWL technology has developed rapidly. Advancements include the development of different power sources, coupling mechanisms, and localization systems. Among the new lithotriptors was the Piezolith 2300, the geometric design of the power source and focusing system of which permitted piezoelectric lithotripsy to be carried out without anesthesia or pain medication, which was a breakthrough in ESWL treatment at the time. However, the efficacy of this machine was never as high as that of the HM-3. [89] The development of lithotriptor technology has continued with the aim to produce an ideal lithotriptor. However, have the modifications resulted in an improvement in efficacy?

A prospective randomized study of lithotriptor outcomes is difficult; hence, there are very few reports on this topic. [91, 159, 169] The main reasons are the financial and spatial difficulties involved in installing two or more machines at the same time for a randomized study. Portis et al. introduced an innovative approach, matched-pair analysis, to try to overcome these problems. [165] They carried out a comparison of the treatment outcomes of a new lithotriptor, the LithoTron, with those of the HM-3, which were obtained from a pre-existing database. This method allows confident comparison of treatment outcomes of different machines with a small sample size.

Facing the same problem, the assessment of the treatment outcome of a new lithotriptor, we opted to perform a similar matched-pair analysis using a retrospective analysis of a contemporaneously collected database. The matching criteria of Portis et al. were used together with additional anatomical factors, as many authors have stressed the importance of the effect of caliceal anatomy on lower caliceal stone clearance after lithotripsy. [136, 142] Among the parameters, CPH seems to be less affected by measurement error, [101] therefore, we decided to incorporate this factor in the matching process. Similarly, for lower ureteric stones, the distance of the stone from the VUJ may affect the likelihood of stone passage and thus it was also included in the matching process. The results showed that 75% of the paired lower caliceal stones had an absolute difference in CPH within 2 mm. For lower ureteric stones, the difference in LUH in three out of the four cases was within 1 mm. By including these anatomical factors, we felt more confident about the degree of matching between the two groups of stones.

Body mass index (BMI) was not included as a matching factor, as suggested by Portis et al., as it was not recorded in the original database of the Piezolith 2300. This points to the importance of database design in collecting data for clinical analysis.

Problems with this type of comparative study, such as the effects of stone composition on treatment outcome, the learning curve of the operator, and the matching of continuous variables, have already been addressed by Portis et al.. The study may also be criticized for the relatively small sample size and theoretically, a sample with a statistical power of 80% and two-sided significance level of 5% needs more than 130 cases. [170] Similarly, based on the data in Table 11.4, the estimated sample size to prove a difference for fragmentation and stone free rate of the two machines would be 111 and 265 cases per arm, respectively. However, this number was impossible to obtain in a limited trial period (usually lasted for few months). For example, for the study performed by Portis *et al.*, in whose study only 38 matched pairs were identified in the five-month trial period. In real life, it is very difficult to obtain a trial machine for a prolonged period. Therefore, the sample size is limited, but the use of the matched-pair approach provides more confidence in the results than does simple comparison. Although this method may not give a clear indication that a machine is better, it does permit the conclusion, in these tightly controlled matched pairs, that the new machine is not vastly superior to the old one.

There are several possible reasons for the failure of the Piezolith 3000 to demonstrate a marked improvement in outcome, one of which is the smaller focal zone. Although a smaller focal zone provides a more precise delivery of shock waves, the stone may not remain in the focal zone during treatment. The high success rate for the HM-3 is believed to be partly related to its large focal zone (15 mm x 90 mm). The difference in the coupling mechanism could also affect the efficacy, as a water cushion can decrease the energy transferred by 15-25%. [86] Another possible factor is the orientation of the generator source. With the Piezolith 3000, the therapy head can only be moved horizontally on an angle from +50 to -60 degrees, which results in entry of the shock waves through the lateral flank of the patient, instead of more directly, from behind, as with the Piezolith 2300. A more oblique and thus longer blast path results in more attenuation of the shock waves before they reach the stone.

The inclusion of fluoroscopy in the Piezolith 3000 facilitates the localization of ureteric stones during lithotripsy and is a significant advance on the Piezolith 2300. However, as upper and mid-ureteric stones were not included in the analysis, comment cannot be made on their treatment outcome. The results showed that for renal and lower ureteric calculi, the addition of fluoroscopy did not seem to improve the outcome, but this may be related to the experience of the staff members, who are highly experienced ultrasonographers and prefer to use ultrasound for stone localization. Nevertheless, fluoroscopy may well be a valuable addition for those operators less familiar with ultrasound imaging, in addition to permitting localization of upper and mid-ureteric stones.

One of the advantages of piezoelectric lithotripsy is the low requirement of analgesia or sedation. The findings of this study indicated that the Piezolith 3000 caused more pain than did the Piezolith 2300, which may be related to the smaller size of the aperture of the new machine (26 cm) compared with that of the old one (30 cm).

Since the introduction of the HM-3, there have been many developments in lithotriptor design. However, the efficacy of the newer machines has yet to match that of the HM-3. This study has shown that, despite further modifications in design, the latest generation of piezoelectric lithotriptors produces treatment outcomes that are no better than those of the previous generation, which is a recurring theme throughout the evolution of ESWL.

V Conclusion

The results of this study showed that despite the significant modifications in lithotriptor design and incorporation of new technology, the latest piezoelectric lithotriptor does not have a treatment outcome better than that of the previous one. The study also demonstrated that matched-pair analysis can help in comparing the outcome of a new machine or technical modification with that of a previous one, with the result obtained by using a database of an established system. This approach is especially useful when the number of treatment cases of the new system is limited because of such reasons as a limited trial period or limited resources for a large-scale study.

Table 11.1 Specifications of the two machines

	Piezolith 2300	**Piezolith 3000**
Generator source	Piezoelectric – single layer	Piezoelectric – double layer
Focusing method	Spherical dish	Spherical dish
Aperture (cm)	30	26
Focal distance (cm)	10-12	15
Peak pressure at focal point (MPa)	120	132
Focal zone (W x L, mm)	2.5 x 30	3 x 16
Energy setting	8 levels	20 levels
Shock rate	1-4 Hz	1-2 Hz
Coupling system	Limited water bath	Water cushion
Imaging system	Coaxial ultrasound	X-ray and coaxial ultrasound

Table 11.2 The characteristics of the stone treated by Piezolith 3000 and the matched stone treated by Piezolith 2300

Original stone treated by Piezolith 3000								Matched stone treated by Piezolith 2300				
Sex	Side	Sites	Maximum diameter (mm)	Minimum diameter (mm)	CPH (mm)	LUH (mm)	Stone Free at 3 month	Maximum diameter (mm) (Blanket are the difference in size from original stone, mm; + larger than, + smaller than)	Minimum diameter (mm)	CPH (mm)	LUH (mm)	Stone Free at 3 month
M	L	UC	3	2			No	3	2			Yes
M	L	MC	9	4			Yes	9	3 (-1)			No
M	L	MC	4	3			No	4	3			Yes
F	R	LC	7	3	26		Yes	6 (-1)	4 (+1)	25 (-1)		Yes
M	L	LC	6	6	23		No	7 (+1)	7 (+1)	23		Yes
F	R	LC	9	6	22		No	8 (-1)	7 (+1)	24 (+2)		Yes
M	R	LC	15	8	25		No	15	8	19 (-6)		No
M	R	LC	7	5	25		Yes	7	5	25		Yes
M	L	LC	4	2	25		No	5 (+1)	3 (+1)	25		No
F	L	LC	5	2	18		No	5	2	17 (-1)		Yes
F	L	LC	9	5	33		No	10 (+1)	5	31 (-2)		No
M	L	LC	6	2	25		Yes	5	3 (+1)	25		No
F	L	LC	4	3	27		No	5 (+1)	4 (+1)	19 (+8)		No
F	R	LC	14	8	48		No	15 (+1)	8	26 (+22)		No
M	L	LC	11	7	29		Yes	11	8 (1)	28 (-1)		No
M	R	P	12	9			No	12	9			Yes
M	L	P	7	4			Yes	7	4			Yes
M	R	P	12	10			No	12	10			No
M	L	P	10	6			Yes	10	6			No
M	L	UU	15	8			No	14 (-1)	9 (+1)			No
M	L	UU	8	6			Yes	8	6			No
M	R	LU	8	4		80	No	7 (+1)	5 (+1)		55 (-25)	Yes
M	L	LU	5	3		44	Yes	5	2 (-1)		44	Yes
M	R	LU	7	5		38	No	6 (-1)	4 (-1)		39 (1)	No
F	R	LU	6	4		45	No	5 (-1)	3 (-1)		44 (-1)	Yes

M-male, F-female, L-Left, R-Right, UC-Upper calice, MC- Mid-calice, LC-Lower calice, P-Pelvis, UU-Upper ureteric, LU-Lower ureteric

Table 11.3 Difference in size of the stones treated by the two machines

Parameter	Measurement (mm)
Maximum diameter	
Exact match	14
Mean – Piezolith 2300	8.04 (3-15)
Mean – Piezolith 3000	8.12 (3-15)
Mean difference (Piezolith 3000 – Piezolith 2300)	0.04
Mean absolute difference (Piezolith 3000 – Piezolith 2300)	0.44
Minimum diameter	
Exact match	12
Mean – Piezolith 2300	5.2 (2-10)
Mean – Piezolith 3000	5.0 (2-10)
Mean difference (Piezolith 3000 – Piezolith 2300)	0.2
Mean absolute difference (Piezolith 3000 – Piezolith 2300)	0.52
Exact match in both diameters	10

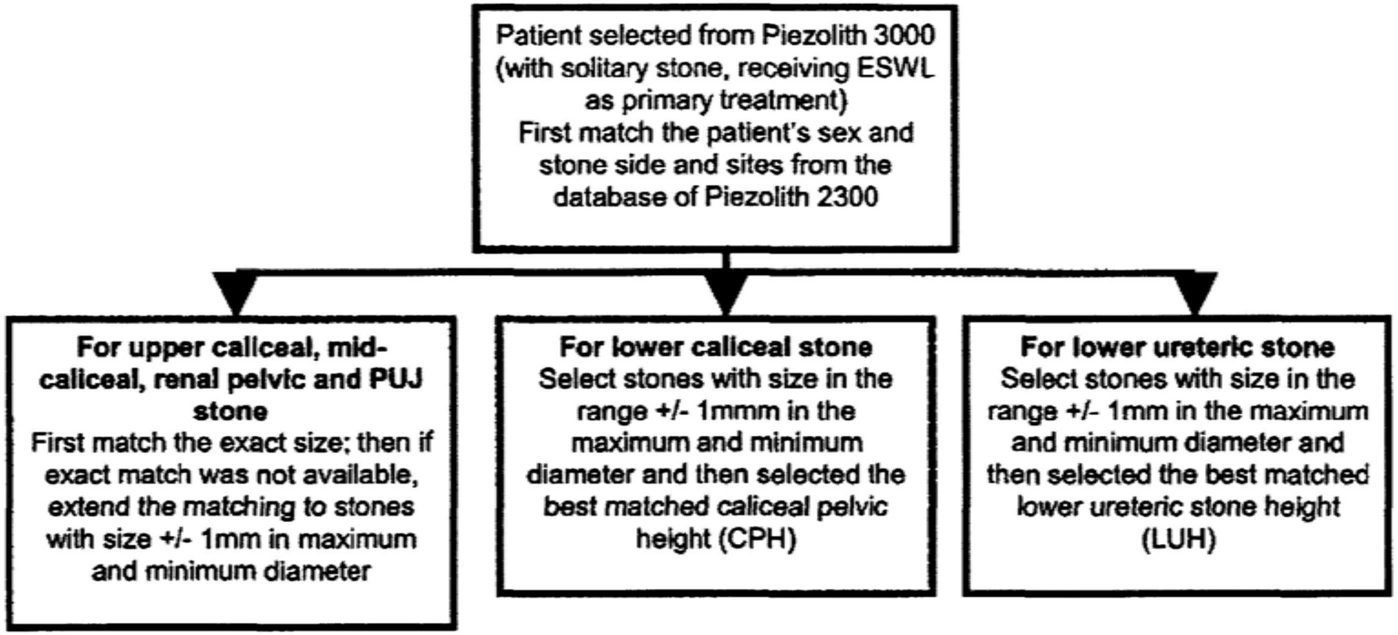
Table 11.4 Overall immediate stone fragmentation rate and stone-free rate at three months

	Piezolith 2300	Piezolith 3000	P value
Fragmentation rate	84%	68%	0.388
Stone-free rate at three months	48%	36%	0.581

Table 11.5 Classification of the treatment outcomes for the matched pairs according to machine and outcome

Initial stone fragmentation		
	Piezolith 2300 – yes	Piezolith 2300 – no
Piezolith 3000 – yes	13	4
Piezolith 3000 – no	8	0
Stone-free rate at three months		
	Piezolith 2300 – yes	Piezolith 2300 – no
Piezolith 3000 – yes	4	5
Piezolith 3000 – no	8	8

Figure 11.1 Flow chart of the steps in the matching of stones.



Upper and mid-ureteric stones were not included for matching.

Figure 11.2 The measurement of caliceal pelvic height (CPH).

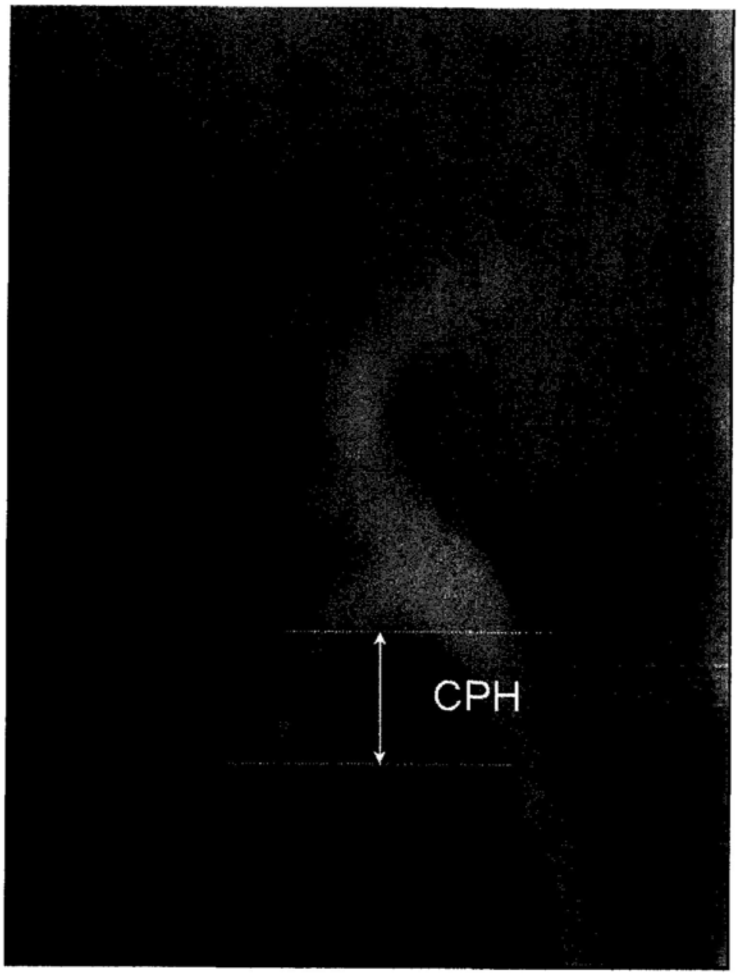
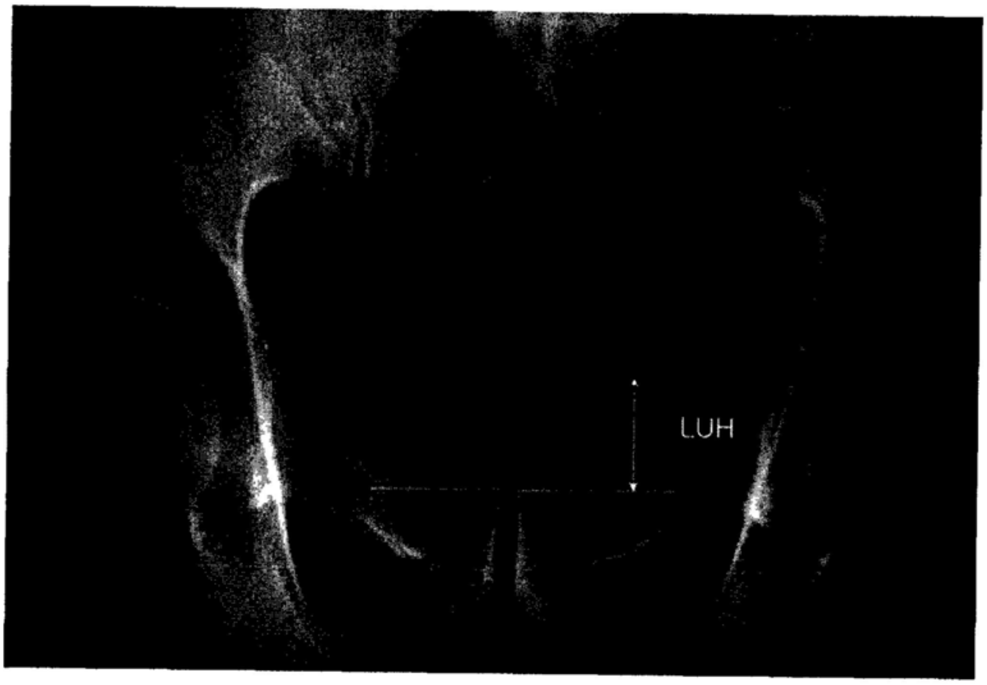


Figure 11.3 The measurement of lower ureteric stone height (LUH).



Chapter 12

Conclusion

This series of investigations demonstrated how we can apply our knowledge to improve the outcome of ESWL. The advantages of these studies include the large sample size and single-center experience. The second study was done in the Lithotriptor and Uro-investigation Centre, Prince of Wales Hospital, Hong Kong, but all of the others were based on data from the Scottish Lithotriptor Centre, Western General Hospital, Edinburgh. As stone cases are not exactly the same, with each varying in terms of patient and stone parameters, the use of a large sample size can provide a better statistical analysis of the effects of individual variables. Also, as the treatment protocol and operator experience also affect the treatment outcome, reports based on single-center experience are more reflective of the actual effects of individual machines and treatment modifications. However, the drawback of the large sample size is the difficulty in performing a prospective study because of the long study period. Except for the second study, for which non-contrast computerized tomography (NCCT) was done in a prospective manner, the studies were based on a retrospective review of data. Nevertheless, as the material in the database was collected from the establishment of the Scottish Lithotriptor Centre in a prospective manner and maintained by the same group of staff during the study period, the potential bias introduced by a retrospective review should be minimized.

In the first study, elderly patients with renal stones were found to have a poorer treatment outcome than younger ones. The large sample size in this study, together with support for our results in the literature, made this observation quite definite. This finding will help in deciding the optimal treatment protocol for patients. In particular, alternative treatments should be considered for elderly patients with other unfavorable factors, such as larger stone size or lower caliceal stones. The reason for this observed effect of age is still unknown, although an effect of nephrosclerosis associated with aging on the transmission of shock waves has been postulated. Previously, there was no good method to quantify different degrees of nephrosclerosis. However, the rapid development of elastography, by ultrasound or magnetic resonance (MR), may provide a way to quantify the degree of renal scarring.[171-174] Prospective studies of the degree of renal scarring and ESWL outcomes could provide further understanding of the effect of the mechanism of aging on ESWL.

In the second study, stone parameters that were measured by NCCT, including mean stone density, stone volume, and skin-to-stone distance, were shown to be useful in the prediction of the stone-free rate (SFR) of patients with upper ureteric stones. A scoring system based on the combination of these three stone parameters was shown to be able to differentiate among patients with different treatment outcomes. The inclusion of a pure stone group, such as upper ureteric stones, could help to avoid other potential confounders that can affect treatment outcomes, such as anatomical factors. As NCCT is currently the investigation of choice for patients with suspected ureteric colic and upper ureteric stones, this study serves to develop from our research knowledge a practical guideline that can be integrated into real clinical practice. When a patient presents with ureteric colic, an NCCT can help in not only diagnosing ureteric stones but also guiding clinical decision making. Further studies are needed to verify the usefulness of this scoring system in other cohorts of patients.

The applicability of caliceal pelvic height (CPH) among different lithotriptors was assessed in the third study. The results showed that CPH was useful in the prediction of the treatment outcome of lower caliceal stones treated by the Piezolith 2300 but not the other two lithotriptors. The results suggested that the usefulness of CPH in predicting treatment outcome was machine dependent. This study helps to explain the controversy over the use of various lower pole anatomical parameters to predict the treatment outcome of lower caliceal stones. Although some reports suggest newer approaches to predict the treatment outcome of such stones, such as the pattern of dynamic urinary transport of the lower calices [139] and use of artificial neural networks, [175] these approaches may not be clinically practical. Therefore, further studies to look for alternative approaches to predict the treatment outcome of lower caliceal stones are needed.

In the fourth study, the current practice of using less potent analgesia for ESWL was revisited. We found that the additional usage of intravenous analgesia during treatment could improve treatment outcomes, compared to oral analgesic premedication alone. Therefore, a policy of more generous usage of analgesia during ESWL is recommended to improve treatment outcomes. Also, further study of factors that can predict analgesic demand during ESWL would be helpful for tailoring the analgesic protocol of individual patients.

Two statistical approaches, logistic regression and matched-pair analysis, respectively, were used in the last two studies for the comparison of the treatment outcomes of different lithotriptors. New machines and treatment methods are continually emerging, and these two approaches provide a fair and standard comparison between new and old systems under different clinical scenario. Logistic regression approach will be suitable for the comparison of different machines / treatment protocols with comparable number of treatment records. For the matched-pair analysis approach will be suitable for the comparison of a new machine on trial with an existing database. These assessment approaches are better than simple comparison of the treatment results of two groups of data, and can adjust the effect of other factors on treatment outcomes. These assessment methods are crucial for the continued development of ESWL to ensure that new technology / treatment protocol can really lead to an improvement in the treatment outcome of ESWL.

Finally, this series of studies revealed important points for consideration in the future development of ESWL. As shock wave technology has been in clinical use for less than 30 years, many related issues are still not fully understood. A critical approach to the assessment of clinical observations, such as the possible effect of age on outcome, as we demonstrated, should not be overlooked. Also, daily practices, such as the trend towards using simple analgesia for treatment, should be revisited and reassessed. Doing so will provide opportunities to better understand ESWL technology and improve treatment outcomes. Another example of the importance of revisiting current practice is the case of dry coupling during ESWL. In a series of excellent studies, a group from the Indiana University School of Medicine demonstrated that the air pockets trapped between the therapy head and generator body can affect the treatment result, and that a more careful application of gel can help to minimize this effect. [176, 177] There are still many areas in the treatment protocol are not answered at this moment, such as the optimal shock wave delivery rate for treatment, the way to start ESWL in order to minimizing kidney injury, the role of medical adjuvant therapy in helping stone clearance etc. A critical and open-minded approach to clinical observation and practice, together with the use of fair and standard assessment, is crucial for the continued development of ESWL.

Also as discussed in the initial part of this thesis, there are still many other areas that required further investigations. Despite there are many new machine designs available in market, such as new generator design, dual generator heads machine, continue stone monitoring device etc. Unfortunately, large-scale multi-centre clinical trials on these new developments are lacking. Therefore, the real impacts of these designs are still uncertain.

In addition, the advancement of medical knowledge, imaging technology, and understanding of ESWL will help to improve the application of ESWL. As shown in this thesis, the wider availability of NCCT has led to the identification of new parameters for the prediction of ESWL outcomes. However, this new knowledge needs to be translated into clinically applicable knowledge to benefit patients, by such means as formulating practical guidelines based on the results of NCCT. Also, as machines are not the same and centers may have different treatment protocols, one important step in the development of such guidelines is the testing of their generalizability. For example, this thesis showed that the usefulness of caliceal pelvic height in predicting the treatment outcome of the Piezolith 2300 was not replicated in other machines. Therefore, practical and generalizability issues need to be addressed for the further development of new parameters in patient selection for ESWL.

The incidence of upper tract urinary calculi, a common disease in affluent and developed countries, is expected to rise in Hong Kong and mainland China. As the majority of patients who suffer from the disease are males aged 30-60 years, normally the most important years of one's career, the potential loss in terms of socioeconomic productivity should not be underestimated. Effective management of urolithiasis is thus vital for both health care and the economy. The minimally invasive nature of ESWL and short recovery time are particularly beneficial to patients. Although the performance of the latest machines has never been as good as that of the first-generation machine, further understanding of the technology will help to improve the performance of the former to recapture the initial success of ESWL. Hopefully, the findings of this thesis will contribute to the continued improvement of ESWL, and benefit patients suffering from urolithiasis.

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LIST OF PUBLICATIONS RELATED TO THE THESIS

Chapter 6

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