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How to maximize the extracorporeal efficacy of shockwave lithotripsy

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بسم الله الرحمن الرحيم

(نَرْفَعُ دَرَجَاتٍ مَّن نَّشَاءُ وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ..)

صدق الله العظيم

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الاهداء

الاهداء اولآ الى وجه الله تعالى

في جميع مراحل الحياة يوجد أناس يستحقون منا الشكر والتقدير واولى الناس بالشكر

والدي العزيز الذي جرع الكأس فارغا ليسقيني قطرة حب

والدتي العزيزة التي وضعتني على طريق الحياة وكان لها الفضل الكبير لنجاحي

والى جميع من وقفوا بجانبي وساعدوني وبالخصوص

الى أصدقائي والى جميع اساتذتي الكرام بوجه عام والى الدكتور

"الأستاذ وليد خالد محمد " المشرف على البحث بوجه خاص الذي كان له دور كبير في اعطائي المعلومات القيمة اهدي لكم بحث تخرجي المتواضع وأتمنى ان تحوز على رضاكم.

ألشكر والتقدير

الحمدلله ألذي هدانا وأعدنا وأمدنا والهمنا الصبر على المشاق ووفقنا لما نحن عليه

فله الحمد والشكر ابتداءاً وانتهاءاً

وارفع كلمة الشكر الى الدكتور وليد خالد محمد

وفقه الله فقد كان سندا لي على طول الطريق

والى كل من مد يد العون لي من قريب او بعيد

وقبل ان امضي اقدم اسمى ايات الشكر والامتنان والتقدير والمحبة

الى الذين مهدوا لي طريق العلم والمعرفة

Abstract

Since its introduction in the early 1980s, extracorporeal shockwave lithotripsy (ESWL) has proven to be a minimally invasive and efficient procedure for the management of renal calculi. It is currently one of the most recommended treatments for small- and medium-sized stones (<20 mm) in most guidelines internationally. The recent coronavirus disease 2019 (COVID-19) outbreak could lead to a further increase in ESWL use as it avoids a general anesthetic and its potential complications in patients with COVID-19 infection. Most publications exhibit ESWL stone-free rates (SFRs) of 70%–80%; however, this is often not the case in many centers, with multiple factors affecting the efficacy of the intervention. Various stone and patient factors have been shown to influence the ESWL success. Stone position, density and size, skin-to-stone distance, and body-mass index contribute to SFRs. Modifications in the lithotripter design and revisions in the technique have also improved the SFRs over the years, with slower shock rates, power-ramping protocols, combined real-time ultrasound, and fluoroscopy imaging technology, all enhancing the efficacy. The adjuvant use of pharmacological agents, such as alpha-blockers, potassium citrate, and the emerging microbubble technology, has also been investigated and shown promising results. Arguably, the most significant determinant of the success of ESWL in a particular unit is how the lithotripsy service is set up and monitored. Careful patient selection, dedicated personnel, and post-treatment imaging review are essential for the optimization of ESWL. Through an analysis of the published studies, this review aimed to explore the measures that contribute to an effectual lithotripsy service in depth.

Contents

١.1. Introduction

Extracorporeal shockwave lithotripsy (ESWL) has been one of the mainstays in the management of renal and ureteric calculi since its inception in 1984. It is currently one of the most recommended treatment options for small- and medium-sized stones in most guidelines and the preferred treatment modality in the United Kingdom's National Institute Clinical Excellence guidelines [1]. The use of ESWL picked up in 2006 but has been in decline because many urologists switched to endoscopic surgical treatments, especially ureteroscopy and laser fragmentation [2]. Nevertheless, ESWL has been shown to be more cost effective than endoscopic surgical treatments, which is the driving factor behind it being recommended as the preferred treatment for various types of stones in many countries [1]. In addition, the recent coronavirus disease 2019 (COVID-19) outbreak may lead to a further increase in ESWL use as it avoids a general anesthetic (GA) and its potential complications in patients with COVID-19 infection,[3] with many centers trying to avoid GA use for less urgent cases. Most publications demonstrate a stone clearance rate of 70%–80%, but this is not often the case in many centers that offer ESWL [4–6].

Extracorporeal shock wave lithotripsy (ESWL) was introduced into medical practice in the 1980s, and since then has become one of the main treatment options in patients with renal and/or ureteral calculi. However, the progress of endourology and minimally invasive surgeries with their high success rates has reduced its applicability. From then on, it has become necessary to search for the optimal technical parameters and careful selection of candidates for ESWL in order to optimize its results and justify its indication [7].

A careful review of the literature discloses that results of extracorporeal shockwave lithotripsy (ESWL) vary considerably from one center to another and from one operator to another. As a consequence of occasionally poor treatment results, we can notice that the popularity of ESWL has decreased during the past decade. This development is to a large extent explained by the technical development of instruments for endoscopic procedures and increased skill in the application of these techniques, but this development is also a result of insufficient attention to the basic principles of how ESWL should best be carried out. As for every surgical procedure, it is important to apply proper indications for urinary tract stone removal with ESWL. The important lesson learnt was that when the original Dornier HM3 lithotripter concept was abandoned and replaced by various later generation devices, the treatment, contrary to what was expected, became more difficult. It has been shown that strict control of a number of factors is fundamental for acceptable treatment results [8, 9, 10].

Neglecting these principles is certainly one of the most important factors that explain why during recent years, numerous ESWL centers have failed to repeat the successful treatment results obtained with the HM3 equipment [11, 12, 13, 14, 15].

It is important to understand that in similarity with other surgical and medical procedures, ESWL requires considerable skill and expertise by the operator [16, 17, 18].

To reach the therapeutic goal of efficient stone disintegration without increasing the risk of complications, it is necessary to make an appropriate selection of patients and, moreover, to pay careful attention to several important factors. For this purpose, it is important to obtain a careful medical history and to carry out the basic examination of the patient. Based on the details of the stone situation, anatomical features and possible risk factors, it is extremely important to inform the patient that repeated treatment sessions occasionally might be necessary and that repeated SWL should not be considered a failure but a consequence of the physics behind non-invasive stone disintegration [19]. With these pre-requisites, it is possible to carry out lithotripsy in a safe and harmonic way, also for patients with complicated stone situations. It is important not to fulfil any unrealistic goal by attempts to complete every stone treatment with only one session using excessive number of shockwaves and/or unnecessary high and risky energy levels. Although experience has shown that the frequency of complications recorded after ESWL is lower than that recorded with endoscopic and open surgical procedures, particular attention must be paid to the risk of developing renal subcapsular hematoma [20, 21, 22], other types of trauma to the kidney [23], injuries to surrounding organs, problems associated with infected urine or stones as well as consequences of urine flow obstruction caused by stones and fragments.

The aim of Study

The aim of the present study to find out How to increase the efficacy of shockwave lithotripsy and what Factors affecting the increase in efficiency.

Stone and patient factors

Multiple stone and patient factors have been shown to affect the efficacy of ESWL. These include stone position, anatomy of the collecting system, skin-to-stone distance (SSD), stone density measured in Hounsfield units (HU), stone size, habitus, body-mass index (BMI) of the patient, and the presence of a ureteric stent (Table 1). **Table 1 : Patient-related factors and scoring systems**

Patient-related factors	Included in Triple D	Included in S3HoCKwave
Stone position	No	Yes (renal/ureteric)
Stone size	Yes	Yes
Skin to stone distance	Yes	Yes
Infundibular angle/length	No	No
Patient habitus	No	No
Stone density	Yes	Yes
Presence of stent	No	No
Sex	No	Yes

Larger stones require more energy to be broken up and leave behind larger fragments. Early studies demonstrated that stone size severely affected the stone-free rates (SFRs) [24]. Showed that SFRs ranged from 94% for calculi <5 mm to 11% for patients with a stone burden of 2 cm or higher. In most guidelines, stones are categorized into 3 groups on the basis of size (<10 mm, 10–20 mm, and >20 mm), with ESWL mainly recommended for the first 2 groups.

Stone density measurements on computerized tomography of the kidneys, ureters, and bladder (CT KUB) were also studied to assess for any correlation with SFRs. Harder stones (brushite, calcium oxalate monohydrate, cysteine, and so on) are more resistant to ESWL. Mean HU measurements on non-contrast CT are commonly used to estimate a stone's hardness and hence its susceptibility to treatment using shockwave lithotripsy. El-Assmy et al [25].considered HU and found that ESWL for stones with >900 HU on low-dose CT KUB was less successful. As the composition of renal calculi is heterogeneous, HU measurements using the mean value for the whole stone may be misleading. Lee et al [26].measured the stone heterogeneity index, calculated as the standard deviation of HU measurements on non-contrast CT, in an attempt to see if it is useful in predicting ESWL success rate in stones with similar mean HU. The authors demonstrated that radiological heterogeneity of stones is an independent predictor of ESWL success in patients with ureteral stones.

SSD was also found to influence SFRs. Several studies considered this and found that an SSD of <9 cm was associated with favorable ESWL outcomes [27, 28].However, a study on 597 Japanese patients by Yoshioka et al.showed that being underweight (BMI<25) had a significant negative association with success of a single-session shockwave lithotripsy (Odds ratio [OR], 0.25; 95% confidence interval, 0.09–0.69) compared with having normal weight[29]. Overall, in the majority of studies, a longer SSD and higher BMI are associated with less successful ESWL outcomes.

In a study from 2008, Lin et al looked into the relationship between the radiological anatomy of the lower calyx and stone clearance for lower pole calculi. The study used pre-ESWL intravenous urograms to measure the lower pole infundibular length, width, and the infundibulopelvic angle. They then proceeded with ESWL and measured SFRs at 3 months post-treatment, which showed that 44% of the patients were stone free. Stone size (<10 mm, p=0.005) and greater infundibular width (>4 mm, p=0.03) were the significant favorable predictors for stone clearance [30].

Several groups developed predictive scores incorporating the above patient factors to try and identify the most suitable patients for ESWL. Tran et al. developed the Triple D score looking at SSD, stone size, and stone density. A score of 3 was associated with 96% SFR compared with 21.4% for a score of 0 [31]. Yoshioka et al developed the S_3HoCKwave score based on the initials of the predictors (sex, SSD, size, Hounsfield units, colic, and kidney or ureter). This score was shown to predict the ESWL failure after 3 sessions with reasonable accuracy [32].

For ureteric stones, the degree of stone impaction is also thought to be a predictor of ESWL success. Pre-treatment ultrasound scan for markers of severely impacted stones has been shown to be able to predict the success rate of ESWL. Useful markers of impaction include the presence or absence of ureteric jets, degree of hydronephrosis, restrictive index measurements, and ureteric wall thickness [33].

Yazisi et al reported a beneficial effect of pre-treatment insertion of ureteric stents for treatment of larger renal pelvis calculi (15–25 mm) with ESWL. They demonstrated significantly improved stone clearance rates in the stented vs. the non-stented group (71% vs. 39%, p=0.002). Stented patients also visited the emergency department less frequently and had lower pain scores post-ESWL [34]. However, Shinde et al demonstrated lowers SFRs when a ureteric stent was present (OR, 6.35) [35]. Overall, ureteric stents do not seem to improve the SFRs or lower the number of treatments needed but may reduce the formation of steinstrasse [36].

Lithotripter and stone fragmentation factors

Since the first ESWL machine (Dornier HM-3) was developed in 1984, multiple new lithotripters have been developed to improve the effectiveness of ESWL. Initially, the machines were large, so decreasing their size, improving the ease of transport, and making them less cumbersome were the focus of development. However, unfortunately, these measures lead to a reduction in SFRs. This phenomenon was thought to be because of a narrower focal zone used in the newer machines. Second- and third-generation machines tried to improve the SFRs without compromising on size and mobility, with moderate results. Through the use of wider acoustic lenses, the focal zone of some of the newest machines has widened without compromising the benefits of limited skin contact and reduced pain [37]. The mode of ultrasound wave generation was also associated with improvement in the SFRs. Newer machines using piezoelectric or electromagnetic generators were shown to be more efficient than the older electrohydraulic machines [38,39]. Sohail et al compared the SFRs between newer and older machines used at their center and found a significant improvement of SFRs with the use of newer devices [40] (Table 2).

Table 2: Common types of lithotripter

	Generation	USS enabled	Dual focus	Shockwave generator
Dornier HM-3	1st	No	No	Electrohydraulic
LiteMed LM 9200	3rd	Yes	No	Electromagnetic
Modulith SLX-F2	3rd	Yes	Yes	Electromagnetic
Piezolith 3000 PLUS	3rd	Yes	Yes	Pierzoelectric
Sonolith i-move/i-sys	3rd	Yes	No	Electroconductive

Shockwave delivery rate and shockwave power modifications were also looked at as potential ways of improving the stone fragmentation and minimizing the surrounding tissue injury during ESWL.

Early on, a high rate of shocks was preferred as it allowed for shorter operating times, but as the science underpinning ESWL progressed, many centers tried slower shockwave delivery rates with some success. In a meta-analysis, Kang et al.[41] showed favorable SFRs for low (60–70 shocks/min) and intermediate (80–90 shocks/min) shock rates compared with higher rates (120 shocks/min).

In addition to using a slower rate, power-ramping protocols were assessed to see if they improved the SFRs. Although most studies demonstrated similar SFRs to the traditional protocol, many showed that ramping protocols reduced pain, seemed to protect the surrounding tissue from injury, and reduced the perirenal hematoma rates [42].

Developments in imaging technology also contributed to improved SFRs with ESWL than the traditional fluoroscopy-only setups. Real-time ultrasound is commonly used in many centers. It allows identification of radiolucent calculi, real-time feedback on stone fragmentation, and better targeting accuracy for ureteric calculi. Many newer machines combine fluoroscopy and ultrasound to improve the accuracy of stone targeting during ESWL. Abid et al.[43]compared fluoroscopy-only ESWL with a combination of ultrasound and fluoroscopy using visio-tracking and ultrasound-guided stone locking system, although success with the ultrasound systems was heavily influenced by the experience of the operator. They reported improved SFRs and lower radiation exposure with the combination system. Similar findings were reported in a study by Chen [44] who used a fluoroscopy-guided lithotripter (LiteMed LM-9200) with real-time ultrasound capabilities to show 80% SFRs.

Another technological development in the field of ESWL was the advent of dual-head shockwave lithotripsy machines. The theory behind them was that by targeting the stone from 2 different angles (2 heads), higher shockwave rates, and thus higher energy, could be delivered to the area of interest, thereby improving the fragmentation while minimizing the surrounding tissue damage. Initial studies demonstrated improved SFRs with no increase in complications [45,46]; however, the technology was not widely used and did not make the anticipated impact.

Mechanical percussion has also been studied as an adjunct to ESWL. It has been shown to facilitate stone fragment passage post-ESWL, improving SFRs and reducing complications. Jing et al.[47] studied the effects of the VT300 Mechanical Percussion Lithecbole Couch, a novel device that applies vibrations to the urinary tract. They demonstrated accelerated passage of fragments post-ESWL with overall higher SFRs and lower need for additional interventions. Other ways to achieve a similar effect without the need for specialized equipment have also been explored. A study by Li et al. [48] found sexual intercourse to be beneficial post-ESWL. They demonstrated that having sexual intercourse 3 times per week post-ESWL could effectively improve the SFR, reduce the formation of steinstrasse, and relieve renal colic. The effects of sexual intercourse were similar to using tamsulosin post-treatment.

Pharmacological interventions

The adjuvant use of multiple pharmacological agents to try and improve the SFRs post-ESWL has been studied in different centers (Table 3). Analgesics are commonly used during ESWL because of lower pain scores and improved patient satisfaction with the procedure. It was thought that they would also result in improved SFRs owing to less patient movement during the procedure. However, no clear evidence exists linking lower pain scores with improved SFRs; moreover, Bovelander et al.[32] reported that the degree of pain during ESWL did not correlate with higher SFRs. Furthermore, studies looking at the local anesthetic use, such as quadratus lumborum blocks, although demonstrating improved pain scores, did not show improved SFRs.[33]

Table 3 : Pharmacological agents

Agent type	Improves SFRs	Reduces complications	Improves patient experience
Alpha-blockers	Yes	Yes	Yes
Diuretics	No	Yes	Yes
Analgesia	No	No	Yes
Potassium citrate	Yes	Yes	Yes
Microbubbles	Yes	Yes	No

SFR: stone-free rate

Many studies have reported the use of diuretics as an adjunct to ESWL to facilitate stone fragmentation and clearance. Diuresis is thought to cause the formation of a fluid film on the surface of stones assisting fragmentation. Findings regarding this were summarized in a systematic review by Wang et al, The authors found that diuretics seem to facilitate stone fragmentation but only had a small and statistically non-significant positive effect on stone clearance. Diuretics were also shown to reduce the number of ESWL shocks and the total number of sessions needed to achieve stone clearance [49].

The use of potassium citrate to facilitate SFRs post-ESWL has also been studied. The theory behind it was that potassium citrate prevented the growth of residual fragments and also prevented them from aggregating or forming a nucleus for new stones. Soygur et al looked at the effect of potassium citrate on calcium oxalate lower pole calculi. They showed that in patients who were stone free after ESWL and were receiving medical treatment, the stone recurrence rate at 12 months was 0%; untreated patients showed a 28.5% stone recurrence rate ($p<0.05$). Similarly, in patients with residual fragments, the medically treated patients had a significantly greater remission rate than the untreated patients (44.5% vs. 12.5%; $p<0.05$)[50] .

The use of medical expulsive therapy in the form of alpha-blockers, especially tamsulosin, has been controversial with several studies showing conflicting results. The rationale behind the use of alpha-blockers post-ESWL is that it promotes the passage of residual fragments. Most of the randomized control trials and several meta-analyses support the use of tamsulosin after ESWL ,They demonstrate that alpha-blockers seem to improve the SFRs and expedite the expulsion of fragments. Furthermore, they may have a role in reducing the need for analgesics post-treatment[51].

Microbubble technology is emerging as a potential adjunct to ESWL. In this approach, microbubbles can be modified with binding domains, which allow them to attach onto calcium stones. Experiments in animals used a 5-F ureteric catheter to introduce modified microbubbles every 90 seconds during ESWL treatment. Using the microbubble technology, stone fragmentation was faster at lower energy levels than without microbubbles. Furthermore, histological evaluation of the renal and ureteric parenchyma post-treatment showed no evidence of tissue injury. Therefore, microbubbles have the potential to improve the safety and efficacy of all ESWL devices by lowering the energy required to achieve fragmentation [52].

Improving outcomes and preventing complications

1. Shock rate

SFRs and risk of complications are linked to the shock rate of treatment. The rate of shock administration is typically between 60 and 120 per minute. A shock rate of 60 shocks/min has two major advantages: Improved efficacy as a higher frequency decreases the negative pressure of the shock wave and potential decrease in the risk of renal injury [53,54].

Clinical studies have demonstrated up to a 16% improvement treating smaller stones and up to a two-fold improvement treating larger renal stones (>100 mm^2) using a rate of 60 shocks/min *vs.* 120 shocks/min [55- 57].

A rate of 60 shocks/min has also been shown to be beneficial for treatment of ureteric stones with a 16% improved SFR and also decreased need for auxiliary procedures [58]. A recent meta-analysis demonstrated that a rate of 60–70 shocks/min and 80–90 shocks/min had significantly higher success rates compared to a rate of 100–120 shocks/min (odds ratio 2.2 and 2.8 respectively) [59]. If stone fragmentation is more effective, then patients may need less shocks overall which also leads to less parenchyma damage [60].

2. Number of shocks

As the number of delivered shocks per session increases, both the rate of stone fragmentation as well as risk of damage to tissues increases. The specifications of individual lithotripters limit the number of shocks delivered per session but most range between 2000 and 4500 shocks/session. The location of the stone also influences the maximum number of shocks that can be delivered safely. Stones that are not within the shock blast of the kidney can be treated with 4000 or more shocks and for the majority of treatments of upper ureteral and renal stones the range is 2000–3500 shocks [61]. The precise “optimal” number of shocks is not clear, but as the number of shocks delivered increase, the risk of damage to tissue increases [62]. Other factors to consider are energy level, patient body habitus, as well as characteristics of the stone [63]. Certainly once a stone has been adequately fragmented, treatment should be discontinued. Extra caution should be taken when treating patients that are at a higher risk for complications.

3. Ramping

In order to maximize treatment effect and limit surrounding tissue damage protocols of ramping up the energy voltage at the beginning of the treatment or a series of low-energy pre-treatment shocks followed by a pause have been developed. By using a ramping protocol it allows for anesthesia to better manage pain which is important to prevent movement and subsequent decoupling of the shock head [64]. When compared to a fixed voltage protocol ramping improves SFR, while renal damage as measured by urinary excretion of microglobulins is decreased [65-67].

Recently, using a porcine model, it was shown that pretreatment (300–500 shocks) at a low voltage without a pause decreases damage to the kidney [68, 69].

A recent clinical trial supports these *in vitro* results; stepwise voltage ramping was associated with a lower risk of hematoma (odds ratio 0.39) when compared to a fixed maximal voltage protocol [70]. Pretreatment and ramping is thought to cause a vasoconstriction of the parenchymal vessels which may be the mechanism behind the protect effects [71].

Stones should be treated at the maximum energy unless stone fragmentation is clearly seen at lower energy levels. When the shock blast is distal to the kidney the desired vasoconstrictive effect seen with ramping is less relevant as perinephric hematoma is unlikely.

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