

THE ROLE OF ORAL DISSOLUTION THERAPY IN INCREASING THE EFFICACY OF EXTRACORPOREAL SHOCKWAVE LITHOTRIPSY IN PATIENTS WITH LESS THAN 2 CENTIMETERS OF RENAL STONES: A SYSTEMATIC REVIEW

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ABSTRACT

The prevalence of renal stones is about 15% of the population. The trend is increasing with a high recurrence rate of up to 50% in 5 years, demanding a more sophisticated treatment for renal stones. ESWL is a treatment for less than 2 cm renal stones with good outcomes. Although ESWL is a technique with many advantages, many factors contribute to the outcome of ESWL with size and stones density as the most important factor. Oral dissolution therapy (ODT) has been used for decades and its effect on renal stones is beneficial to dissolve and prevent renal stones recurrence. The combination of ODT and ESWL is not yet recommended by current guidelines. The purpose of this systematic review is to summarize the latest evidence on the role of ODT in increasing the efficacy of ESWL for renal stones. The database used in this study are PubMed and Cochrane using keywords “urolithiasis”, “renal”, “shock wave”, “citrate”, and “oral dissolution therapy”. The outcome of the article sought is stone fragmentation after ESWL. 4 studies were included, and 3 compared the outcome between ESWL alone and ESWL combined with ODT. The outcome of combined therapy shows superior outcomes compared to ESWL alone with fewer sessions required for stone clearance or a higher chance for stone fragmentation. One study in children showed 100% stone clearance after ESWL with ODT, which was higher than the average success rate of ESWL in children with renal stones. Oral dissolution therapy may have a role in increasing the efficacy of extracorporeal shockwave lithotripsy for patients with less than 2 cm renal stones.

Keywords: *oral dissolution therapy, extracorporeal shockwave lithotripsy, renal stones, kidney*

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INTRODUCTION

The prevalence of renal stones has witnessed a significant surge, reaching up to 15% in the general population, and this upward trend has been particularly pronounced in the last decade. This escalating prevalence is accompanied by a disconcertingly high recurrence rate, which can soar to 50% within five years without proper preventive measures (Pearle MS, Antonelli JA, 2016). The alarming statistics underscore the pressing need for more advanced and non-invasive approaches to address renal stones, given the anticipated increase in the number of individuals grappling with this ailment.

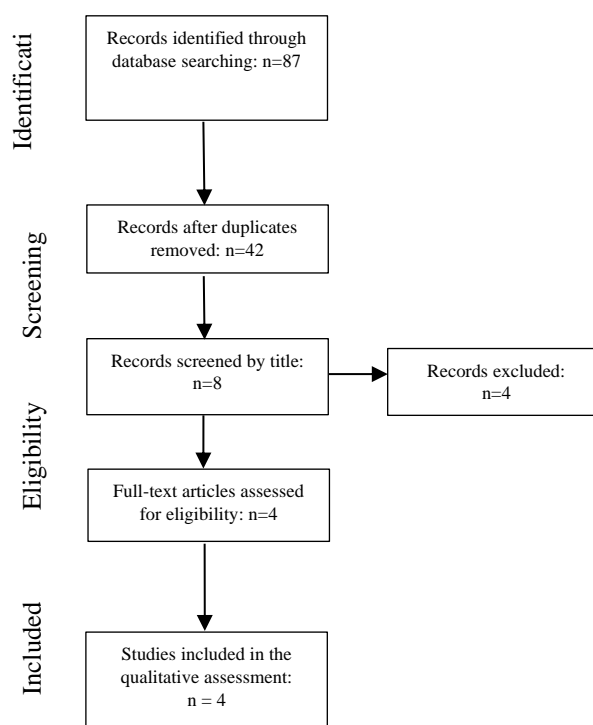
Among the existing non-invasive treatments, Extracorporeal Shockwave Lithotripsy (ESWL) stands out as a promising option, boasting a success rate ranging from 65% to 90%. Notably, ESWL offers the advantage of being conducted through a polyclinic setting, circumventing the complexities associated with surgical preparations. In tandem with ESWL, Oral Dissolution Therapy (ODT) has demonstrated efficacy in dissolving both radiolucent and radiopaque stones to a certain extent. Despite these individual successes, the combination of ESWL and ODT has not received endorsement from current guidelines, primarily due to a lack of robust evidence supporting its efficacy (Massoud et al., 2014).

This dearth of evidence serves as the impetus for the current systematic review, which aims to bridge the existing knowledge gap. The systematic review specifically seeks to identify and analyze studies that compare the outcomes of renal stone treatment using ESWL alone versus a combination of ESWL and ODT (Chung et al., 2016). By focusing on stone clearance and fragmentation as key outcomes, the review aims to contribute valuable insights to the ongoing discourse on optimizing treatment strategies for renal stones.

METHOD

Two database was used in this systematic review, PubMed and Cochrane. The search was limited to English and trial studies. The search terms were “urolithiasis”, “renal”, “shock wave”, “citrate”, and “oral dissolution therapy”. A combination of keywords was used to capture all citations that exist.

The inclusion criteria of the study are patients with renal stones, symptomatic, and functional kidneys. A study that includes pregnant patients, obesity, recurrent UTIs, and abnormal anatomical conditions is excluded. The outcome that is desired is stone clearance and stone fragmentation.



RESULTS AND DISCUSSION

From two databases (PubMed and Cochrane) we found a total of 87 articles. After we removed all of the duplicates and screened through the title we ended up with four studies. These four studies were included based on our eligibility criteria. The four studies included are by Mokhless et al, Goktas et al, Elbaset et al, and del Carmen et al.

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Author	Group	Patient	Stone type and size	Oral Dissolution Therapy	Result
(Mokhless et al., 2009)	ESWL + ODT	Pediatric	<ul style="list-style-type: none"> • Radiolucent • 12-45 mm 	Potassium-Sodium Hydrogen Citrate	100% Stone Free Rate
(Göktaş et al., 2012)	<ol style="list-style-type: none"> 1. Hypocitraturia (ESWL + ODT) 2. Hypocitraturia (ESWL) 3. Normocitraturia (ESWL) 	Adult	<ul style="list-style-type: none"> • Radiolucent • 10-19 mm 	Potassium Citrate	<ul style="list-style-type: none"> • Less session for stone clearance group 1 vs 2 ($p = 0.027$) • Lower time to stone-free status in group 1 vs 2 ($p = 0.043$)
(Elbaset et al., 2020)	<ol style="list-style-type: none"> 1. ESWL + ODT 2. ESWL 	Adult	<ul style="list-style-type: none"> • Radiolucent • 10-25 mm 	Potassium-Sodium Hydrogen Citrate	<ul style="list-style-type: none"> • Higher SFR in 1st, 2nd, and 3rd in group 1 ($p = 0.003, 0.001, 0.003$) • Lower number of ESWL needed in group 1 ($p = 0.001$) • Lower number of auxiliary treatments for group 1 ($p = 0.001$)
(del Carmen Cano García et al., 2023)	<ol style="list-style-type: none"> 1. ESWL + ODT 2. ESWL + Placebo 	Adult	<ul style="list-style-type: none"> • Radiopaque • 17-25 mm 	Hydroxycitric Acid	Group 1 achieved a higher stone fragmentation rate ($p = 0.006$)

Mokhless et al did single-arm trials to analyze the effect of a combination of ESWL and oral Potassium-Sodium Hydrogen Citrate in pediatric patients with radiolucent renal stones. The average size of renal stones is between 12-45 mm. ODT was given to alkalinize the urine to achieve a urine pH of 6.5-6.8 and only then the patients will get ESWL treatment. In this study, all pediatric patients achieved stone clearance in three months of combination therapy. ODT is still being given for 30-50 days. Follow-up was done after 12-36 months and no stones recurrence was noted. Based on stones analysis, all patients had pure uric acid stones.

Goktas et al did a randomized controlled trial to analyze the difference in outcome between three groups of patients with renal stones. Group 1 was hypocitraturia patients with combination therapy (ESWL+ODT), Group 2 was hypocitraturia patients with ESWL only, and Group 3 was normocitraturia patients with ESWL only. This study uses Potassium Citrate as their ODT. All of the patients had radiolucent renal stones with a size between 11-19 mm. The ODT was given in Group 1 until they achieved normocitraturia. ESWL was done in all groups and the result was Group 1 needed fewer sessions for stone clearance compared to Group 2 ($p = 0.027$).

Elbaset et al did a randomized controlled trial to find out the outcome between Group 1 ODT only, Group 2 ESWL only, and Group 3 combination therapy in patients with radiolucent renal stones with stones sizes between 10-25 mm. This study uses Potassium-Sodium Hydrogen Citrate as its ODT. The result was Group 3 had a higher stone-free rate in the 1st, 2nd, and 3rd months after therapy with $p = 0.03, 0.001, \text{ and } 0.003$, respectively.

del Carmen et al did a randomized controlled trial in patients with radiopaque renal stones with a size between 17-25 mm. There are two groups in this study, Group 1 is ESWL+ODT and Group 2 is ESWL+Placebo. They use Hydroxycitric acid as the ODT for Group 1. The result after therapy was a higher stone fragmentation rate in Group 1 compared to Group 2 with $p = 0.006$.

Discussion

The result of our systematic review shows that the addition of ODT will significantly improve the efficacy of ESWL in patients with renal stones. Even in patients with radiopaque stones and hypocritaturia condition. This result will further add the proof needed to update the guidelines for renal stone treatment with ESWL. Below is the discussion on how the ODT can improve the efficacy of ESWL.

Stones Formation

The formation of kidney stones occurs due to an increase in urine supersaturation, which results in the formation of crystal particles. Supersaturation is the main factor in the crystallization of particles in solution. If a solvent contains soluble salt, the solvent will continue to dissolve the salt until it reaches a certain concentration when dissolution will not occur and crystals will form. Without an effective crystallization inhibitor, kidney stones will form. The inhibition factor allows the urine solution to maintain high concentrations of calcium dissolved and not form crystals. Therefore, urine is considered metastable for calcium. Individuals who have a history of kidney stones produce urine with a higher calcium saturation compared to individuals who do not have a history of kidney stones (Alelign & Petros, 2018). The transit time of around 5-10 minutes from the kidneys to the bladder is believed by experts to be too short to start crystallization, this shows that stone formation begins with increasing solute saturation with the failure of the inhibitor factor, and crystallization occurs (Moe, 2006).

Inhibitors are compounds that can increase the threshold concentration of a dissolved substance in the urine for supersaturation to occur and nucleation, inhibit the growth rate and aggregation of crystals and inhibit secondary nucleation⁹. These inhibitory factors are divided into inorganic and organic. Abnormal function or concentration of this compound in the urine can cause urinary tract stone formation to occur more easily. Examples of inorganic inhibitory factors are citrate, magnesium, and pyrophosphate. Organic inhibitory factors include Tamm-Horsfall protein, osteopontin, glycosaminoglycan, and adequate urine production (Hamamoto et al., 2011).

Effect of oral dissolution therapy on renal stones

Although the use of minimally invasive techniques has changed the approach to treating urinary tract stones by ensuring their effectiveness and safety, there has been a significant increase in the importance of medical therapy initiated by the metabolic abnormalities present. When treatment of metabolic disorders is performed before, concurrently, and after surgical intervention, this method has been shown to increase stones-free rates, reduce stone recurrence rates, reduce kidney damage, and reduce postoperative morbidity (O.W. et al., 2011). Given the numerous studies demonstrating the influence of metabolic abnormalities on urinary tract stone formation, the integration of adjuvant medical therapy with minimally invasive approaches for the treatment of urinary tract stones appears to be a promising area for further research (Aggarwal et al., 2013).

Oral dissolution therapy for kidney stones is mostly composed of citrate or citrate derivation. The use of citrate supplementation as oral dissolution therapy has been proven to be able to dissolve and prevent the formation of kidney stones in radiopaque and radiolucent kidney stones (Chung et al., 2016; Shastri et al., 2023).

Citrate is thought to be able to influence the crystallization process of calcium oxalate monohydrate and calcium phosphate. The most obvious effect of citrate in urine is that it binds to free calcium, thereby reducing the possibility of calcium binding to oxalate. This not only occurs with free calcium but also on the surface of calcium oxalate crystals that have been formed so that not only does it prevent it, citrate can also break the calcium oxalate bonds and cause a decrease in the surface integrity of the calcium oxalate crystals (Chen et al., 2018). By decreasing the surface integrity of the crystal, the waves from ESWL will be able to work more easily to destroy the stones. Stones that have been fragmented will cause the surface area of the stones to increase and will increase the working effect of citrate to weaken the integrity of the stones (American Urological Association, 2014).

The presence of citrate in the urine will also increase the pH of the urine which will prevent the aggregation of calcium-phosphate-crystals and also uric acid stones. Uric acid stones that are exposed to high pH, apart from being an inhibitory factor, will also reduce the hardness of the stones and can even dissolve the uric acid stones (Pearle et al., 2014).

CONCLUSION

In conclusion, the amalgamation of Oral Dissolution Therapy (ODT) and Extracorporeal Shockwave Lithotripsy (ESWL) emerges as a promising avenue for enhancing outcomes in patients afflicted with symptomatic kidney stones, irrespective of the stone's radiopacity. The collective treatment approach appears to yield superior results when compared to the application of ESWL in isolation. This conclusion is drawn from the observed benefits in terms of improved therapeutic outcomes and enhanced functionality of kidneys. However, it is crucial to note that the current body of evidence supporting this combination therapy is still limited.

To bolster the credibility of these findings and establish a more comprehensive understanding of the benefits, further randomized controlled trials are imperative. The necessity for additional research stems from the acknowledgment that a robust evidence base is crucial for informing clinical guidelines and ensuring the optimal care of patients with renal stones. By conducting more rigorous and well-designed trials, researchers can contribute substantively to the existing knowledge, potentially solidifying the role of combined ODT and ESWL as a preferred treatment modality for symptomatic kidney stones. Ultimately, this pursuit of additional evidence is essential for refining therapeutic strategies and improving the overall management of patients grappling with renal stone-related complications.

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