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Alpha-blockers after shock wave lithotripsy for renal or ureteral stones in adults (Protocol)

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[Intervention Protocol]

Alpha-blockers after shock wave lithotripsy for renal or ureteral stones in adults

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of alpha-blockers as adjuvant medical expulsive therapy in adults undergoing shockwave lithotripsy for renal or ureteral stones.

BACKGROUND

Description of the condition

Urinary tract stones are the result of a complex cascade of events that involves supersaturation of stone-forming salts that precipitate out of solution to form crystals or nuclei. Once formed, these can either flow out and be excreted; or they are retained in the kidney where crystals can aggregate and grow to form macroscopic stones that may cause urinary symptoms and obstruction.

Urinary tract stones are a common urologic problem and the worldwide prevalence and incidence is increasing (Romero 2010). The prevalence has been reported as 16.9% in Thailand, 14.8% in Turkey and 14% in the United Kingdom (Romero 2010; Rukin 2017). In the USA, the prevalence of stone disease has been estimated at 10.6% in men and 7.1% in women (Scales 2012). The cost of this disease is high, with estimates upwards of several billion dollars per year in the USA (Saigal 2005). There are variable costs associated with urinary tract stones based on acute, medical or surgical management options (Canvasser 2017).

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Diagnosis

Patients presenting with clinical suspicion for symptomatic urinary tract stones are evaluated with history and physical examination, followed by imaging studies. The primary imaging modality used depends on the availability of the tool. In a study of patients presenting to an emergency department with a stone, 90% had acute unilateral flank pain, hematuria, and positive imaging by kidney, ureter, and bladder (KUB) radiograph (Elton 1993). However, the European Association of Urology (EAU) recommends ultrasound (US) as the initial diagnostic imaging tool in patients suspected of urinary tract stones due to its safety profile and low cost (Turk 2016). Imaging beyond US may be needed to best characterize the stone and its location. Non-contrast-enhanced computed tomography (NCCT) is the gold standard diagnostic tool. It has been shown to best characterize stone density and determine precise location including defining skin-to-stone distance - factors important in determining the best treatment modality (El-Nahas 2007; Kim 2007; Zarse 2007). NCCT has largely replaced intravenous urography (IVU) in diagnosing acute urinary tract stones due to its higher diagnostic accuracy (Worster 2002).

Treatment

Urinary tract stones may pass on their own or require intervention to assist with expulsion. The likelihood of spontaneous passage depends on the size and location of the stone. Smaller stones located more distally in the urinary tract, notably the distal ureter and beyond, have the highest rates of spontaneous passage (Hubner 1993). Segments of the ureter are defined radiographically: proximal from its origin to the upper border of the sacroiliac (SI) joint; middle overlying the SI joint; and distal from the lower border of the SI joint and beyond. Ureteral stones less than 10 mm have the highest incidence of spontaneous expulsion, and the American Urological Association (AUA) recommends observation with trial of passage in patients whose pain is well controlled and are free of signs of infection or high-grade obstruction (Assimos 2016a; Assimos 2016b). Furthermore, for uncomplicated ureteral colic due to ureteral stones of the distal ureter, these guidelines recommend medical expulsive therapy (MET) with alpha-blockers (Assimos 2016a; Assimos 2016b). A recent panel using GRADE and following the British Medical Journal (BMJ) Rapid Recommendations procedure recommend MET, even in settings when stone size and location has not been established by imaging studies (Vermandere 2018). Supporting evidence for the use of MET as primary treatment for ureteral stones comes from several high-quality reviews (Campschroer 2018; Hollingsworth 2016). It should be noted that MET is an off-label indication for alpha-blockers. Meanwhile patients with a more complicated presentation, for example those with signs of a systemic infection, as witnessed by fever and elevated white blood cell count, should undergo immediate urinary drainage by ureteral stent or percutaneous nephrostomy placement.

Renal colic is a likely symptom of acute stone episodes and must be treated accordingly. Pain management is part of the usual treatment regimen for symptomatic stones. The EAU and AUA recommend non-steroidal anti-inflammatory drugs (NSAIDs) including metamizole to treat renal colic (Assimos 2016a; Assimos 2016b; Turk 2016). Definitive stone treatment may be offered to patients if spontaneous stone passage is not achieved or sooner intervention is clinically necessary. The typical timeframe for a trial of spontaneous passage ranges from four to six weeks. Patients with pain uncontrolled with oral analgesics, worsening renal function or sepsis from the urinary tract require surgical management, either definitive management with stone removal or urinary drainage (in the setting of signs of sepsis) (Assimos 2016a; Assimos 2016b; Turk 2016). Two commonly used options for definitive management are ureteroscopy (URS) and shock wave lithotripsy (SWL). An advantage of URS is the greater stone-free rate, which has been shown even when stones less than 10 mm are stratified by location in the ureter (Preminger 2007). The higher stone-free rate after a single procedure is particularly notable for distal ureteral stones, and thus URS typically is recommended over SWL. Advantages of SWL over URS are decreased complication rates and lower morbidity (Aboumarzouk 2012). The complications of urinary tract infections (UTI), ureteral strictures, and ureteral avulsion are similar between SWL and URS, but URS has a higher risk of ureteral perforation (Aboumarzouk 2012). Additional options for definitive treatment of stones include percutaneous nephrolithotomy (PCNL), laparoscopic, open or robotic surgical removal.

SWL is a noninvasive procedure where high-energy shock waves are applied to the outside of the body to break up urinary tract stones in the kidney and ureter. The tiny stone fragments can then pass through the urinary system to be excreted. To aid in patient comfort, SWL may be performed under mild sedation, or local or general anesthesia. Fluoroscopy or US (or both) are used for imaging studies throughout the procedure to properly localize the stones and monitor treatment progression (Kohrmann 1995). The technique of SWL encompasses a number of factors to optimize treatment outcomes (Matlaga 2016). Modifiable SWL parameters include the number of shocks, period of shock wave administration, voltage, type of shock wave generator and rate of shock wave delivery. In addition, focal zones differ considerably by lithotripter type, manufacturer and model, and can greatly impact stone fragmentation effectiveness. Of note: current evidence-based guidelines only recommend SWL in patients with normal anatomy of the collecting system, normal renal function and the absence of infection. Given its unknown effect on the fetus (especially given the common use of fluoroscopy), SWL is also not recommended in pregnant women (Assimos 2016a; Assimos 2016b; Turk 2016). Further possible complications from SWL of renal or ureteral stones are related to incomplete stone fragmentation and renal colic symptoms when fragments cause distention and obstruction of the ureter (Skolarikos 2006). The term steinstrasse refers to when multiple stone fragments or debris line the ureter (Sayed

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2001). Steinstrasse occurs in 1% to 4% of SWL cases (Madbouly 2002). This complication can lead to clinically significant obstruction, pain and infection (Sayed 2001). Trauma to the kidneys causes bleeding in the urinary tract when SWL is performed. The shock waves cause small vessels in the kidney to rupture which can lead to hematoma formation (Matlaga 2016).

Description of the intervention

Alpha-blockers work by relaxing smooth muscle and help keep small blood vessels open. Examples of alpha-blockers include tamsulosin, alfuzosin, terazosin, naftopidil and silodosin. They are typically used to treat or improve symptoms of high blood pressure and benign prostatic hyperplasia (BPH), and are particularly helpful if a patient has both conditions. Because there is a lack of evidence supporting the cardioprotective effects of alpha-blockers compared to placebo, alpha-blockers are no longer recommended as first-line treatment for high blood pressure (Pool 2005). Alpha-blockers have been shown to improve lower urinary tract symptoms (LUTS), the complex of symptoms associated with BPH (Shapiro 1992). The rationale for the use of alpha-blockers is that LUTS are at least partly due to bladder outlet obstruction (BOO), a process mediated by alpha$_1$ adrenoreceptors in prostatic smooth muscle (Caine 1976).

Alpha-blockers are available as an adjuvant medical therapy to enhance stone fragment passage after SWL. If fragments do not readily pass after SWL, patients can develop complications including steinstrasse as described above. Urinary tract obstruction, infection and significant pain can develop from incomplete stone passage. The use of SWL as treatment for stones may result in need for repeat or additional procedures to clear all stone fragments. Therefore, we are interested in the use of alpha-blockers to facilitate stone passage after SWL. Like MET for improvement of spontaneous stone passage, MET after SWL is an off-label use of the medication in the USA (Campschroer 2018).

Adverse effects of the intervention

The most frequent adverse effects of alpha-blockers are related to the cardiovascular system. The American Geriatrics Society 2015 recommends avoidance of the alpha-blockers doxazosin, prazosin, and terazosin as anti-hypertensive medications in elderly patients due to the high risk of orthostatic hypotension. Because of the risk of orthostatic hypotension, as well as bradycardia, avoidance of use in patients with history of syncope is also recommended (Boehringer 2019). Alpha-blockers may exacerbate heart failure. Tamsulosin has been reported to cause atrial fibrillation in post-marketing studies (Boehringer 2019). Additionally, those studies have reported adverse effects of palpitations, peripheral edema, tachycardia and cardiac dysrhythmia.

Adverse effects of terazosin on the genitourinary tract have been reported. In male patients, erectile dysfunction has been known to occur in 1.2% to 1.6% of patients (Abbott Laboratories 2019). Priapism - prolonged and painful erection of the penis - has been reported, but only very rarely (Abbott Laboratories 2019). Abnormal ejaculation has been reported with alpha-blocker use. In men taking tamsulosin, the incidence of abnormal ejaculation has been reported between 8.4% and 18.1% (Boehringer 2019). The abnormal ejaculation was reversible in 76% of patients upon discontinuation of the drug (Hofner 1999). Decreased ejaculate volume has been reported in 89.6% of men taking tamsulosin, and anejaculation, the lack of any ejaculation, has been reported in 35.4% of men taking tamsulosin (Hellstrom 2006). Furthermore, alpha-blockers may worsen incontinence in women with stress or mixed urinary incontinence (Kiruluta 1981; Thien 1978).

How the intervention might work

The rationale for the use of alpha-blockers as an adjuvant medical therapy for stones is based on the natural history of stones causing contraction of the ureters during passage that may inhibit expulsion. Contractility of the ureters is mediated by alpha and beta adrenoreceptors located in the ureteral walls (Park 2007). The ureters contains alpha$_{1D}$ and alpha$_{1A}$ adrenoreceptor subtypes and the less prevalent alpha$_{1B}$ adrenoreceptor subtype (Itoh 2007; Karabacak 2013; Sigala 2005). The distal ureter contains the highest density of alpha$_1$ adrenoreceptors, as observed based on the ability of the distal ureter to generate a higher contractile force compared to the proximal ureter (Sasaki 2011).

Adrenergic transmission is mediated by the chemical norepinephrine, which is synthesized within neurons. Norepinephrine activates alpha-adrenergic receptors and causes stimulation of ureteral activity (Hernández 1992; McLeod 1973). Stimulation of alpha receptors has been shown to increase contraction of ureteral smooth muscle and promote more frequent peristalsis (Park 2007; Sasaki 2011). Therefore, blockade of alpha receptors with alpha receptor antagonists leads to decrease in ureteral contractions (Rose 1974). The decrease in ureteral spasm by alpha-blockers has the potential benefit of easing spontaneous stone passage of stones by increasing the rate of expulsion and decreasing pain (Crowley 1990; Laird 1997). It is the alpha-blockers that have selectivity for alpha$_{1A}$ adrenoreceptor subtype, namely alfuzosin, doxazosin, prazosin, tamsulosin, terazosin and silodosin, that have primarily been used for medical expulsive therapy.

Pharmacological agents that facilitate ureteral relaxation have the potential to aid in stone expulsion (Sivula 1967). Medications with alpha-blocking activity help to relax ureteral smooth muscle and could aid in stone passage. Other agents that mediate ureteral relaxation through mechanisms other than alpha-blockers (for example: calcium channel blockers) have been explored in enhancing stone passage, but are outside the scope of this review (Gupta 2014; Pickard 2015).

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Why it is important to do this review

Whereas a number of trials have been conducted to assess the effect of alpha-blockers in patients undergoing SWL for urinary tract stones, there is no consensus as to its effects. Underlying issues relate to clinical differences between trials, such as the type of lithotripter and the definition used for successful stone fragmentation as well as varying methodological quality of these trials. These issues mirror those in the use of alpha-blockers in patients with ureteral colic which were addressed in a recent Cochrane Review (Campschroer 2018). Campschroer 2018 and another high-quality review (Hollingsworth 2016) have suggested a possible subgroup effect based on stone size with greater effectiveness in larger stones (≥ 5 mm). This appear relevant to our review given that SWL stone fragments can be expected to be smaller (≤ 3 mm) in size, thereby drawing into question the effectiveness of MET in this setting. Our review will therefore address the specific clinical scenario of alpha-blocker use after SWL. Adjuvant treatment to SWL may provide important benefits for patients with residual fragments after SWL. There is potential to accelerate stone passage, thereby leading to less analgesic use, faster recovery and less time away from work. Adjuvant treatment may also reduce costly and invasive secondary treatments, Alpha-blockers are particularly appealing for MET due to their reported favorable side effect profile and low cost. We expect this review to provide important guidance for individual patients, clinicians, guideline developers and policy makers by rigorously assessing the magnitude of both potential desirable and undesirable effects and our confidence in these estimates of effect.

Existing systematic reviews - Lee 2012; Li 2015; Losek 2008; Schuler 2009; Seitz 2009; Skolarikos 2015; Yang 2017; Zheng 2010; Zhu 2010 - on the use of MET after SWL to date have not applied the same methodological rigor as a Cochrane Review, where we focus on patient-centered outcomes by applying the GRADE approach (Guyatt 2008). Our review is structured to address an ongoing knowledge gap on the effectiveness of MET after SWL in clinical practice.

OBJECTIVES

To assess the effects of alpha-blockers as adjuvant medical expulsive therapy in adults undergoing shockwave lithotripsy for renal or ureteral stones.

METHODS

Criteria for considering studies for this review

Types of studies

We will include parallel-group and cluster randomized controlled trials (RCTs). We will exclude cross-over trials as this study design does not provide a useful framework to capture our outcomes of interest. The defined intervention has unclear benefit in this patient population, and randomization remains an ethical option for study design. Therefore, we will exclude non-RCTs and trials using pseudo-randomization techniques. We will not include single-arm studies or studies without a control arm. We will include studies regardless of their publication status, as identified by published manuscript, abstract or registration database. We will include studies regardless of language of publication.

Types of participants

We will include studies of adult patients (18 years or older) of either gender who have undergone SWL for renal and ureteral stones. We will include trials irrespective of the lithotripter type used, the number of shock waves applied and the number of sessions performed. We will include only studies that use imaging to confirm stone diagnosis. The imaging modality may be a single test - for example, NCCT - or a combination of tests such as KUB radiograph and US.

We will exclude studies on MET for the primary expulsion of stones. We will exclude studies of children and pregnant women. We will also exclude studies of patients with renal insufficiency (defined as an estimated glomerular filtration rate < 60 ml/min/1.73 m²), obstructive uropathy or UTI.

Should we identify studies in which only a subset of participants are relevant to this review, we will include such studies if data are available separately for the relevant subset.

Types of interventions

We plan to investigate the following comparisons of experimental intervention versus comparator intervention. Concomitant interventions will have to be the same in the experimental and comparator groups to establish fair comparisons.

Experimental interventions

- Alpha-blockers and usual care

Comparator interventions

- Placebo and usual care, or usual care alone

Comparisons

- Alpha-blockers and usual care versus placebo and usual care, or usual care alone

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For the purpose of this review, usual care in the context of SWL for kidney and ureteral stones may be used in the alpha-blocker treatment group as long as the same care is also used in the control group. Usual care may include oral or intravenous hydration, NSAIDs, pain medication and antibiotics as deemed clinically appropriate. We will exclude studies that include antispasmodics, corticosteroids or herbal supplements in the usual care regimens as these could potentially alter the treatment effect; this approach is consistent with that of high-quality reviews on MET (Hollingsworth 2016). We recognize that this determination may limit the applicability of our review findings with regard to practice settings in which these adjuvants are commonly used and also limit further exploratory analyses as to their role. However, the main objective of this study are the effects of alpha-blocker, and inclusion of these adjuvant agents pose the risk of adding both noise (random error) and bias to the planned analysis.
We anticipate potential variation in the intra-operative management of anesthetic, sedation, pain, and antibiotics for patients undergoing SWL, but will not consider those factors relevant unless they differ between treatment and control groups.

Types of outcome measures

We will not use the measurement of the outcomes assessed in this review as an eligibility criterion.

Primary outcomes

- Stone clearance (dichotomous outcome)
- Auxiliary treatment (dichotomous outcome)
- Serious adverse event (dichotomous outcome)

Secondary outcomes

- Quality of life (continuous outcome)
- Time to stone clearance (continuous outcome)

Method and timing of outcome measurement

When reviewing outcomes, we will consider clinically important differences by pre-defined thresholds in order to rate the overall quality of evidence in the 'Summary of findings' table (Jaeschke 1989; Johnston 2013). In the absence of published minimal clinically important differences, we will establish thresholds with input from our content experts.

Stone clearance

- Participants with documented passage of all stones from the kidney and ureter of a given size criterion based on imaging (e.g. KUB radiograph, NCCT) as defined by the investigators.
- We will assess this outcome up to 90 days after SWL
- We will consider a 5% absolute difference in stone clearance as clinically important

Auxiliary treatment

- Participants requiring unplanned, additional treatments such as ureteroscopy or stent placement due to failure of stones to pass or to treat secondary complications such ureteral colic or hydronephrosis
- We will assess this outcome up to 30 days after SWL
- We will consider a 5% absolute difference in re-treatment rates as clinically important

Serious adverse events

- Example: syncope or hypotension requiring inpatient hospitalization or unplanned emergency department visit
- We will use the FDA definition of serious adverse events (FDA 2018)
- We will assess this outcome up to 90 days after SWL
- We will consider a 1% absolute difference in serious adverse events rates as clinically important

Quality of life

- Mean change from baseline or final mean value measured using a validated scale. For example, the RAND 36-Item Health Survey (SF-36) (Ware 1992).
- We will assess this outcome up to 90 days after SWL
- We will consider a clinically important mean difference of points on quality of life scores based on the specific scale used

Time to stone clearance

- Length of time from onset of treatment to stone clearance as measured in days
- We will consider a mean difference of 1 day as clinically important

Main outcomes for 'Summary of findings' table

We will present a 'Summary of findings' table that reports on the following outcomes (listed according to priority).

- Stone clearance
- Auxiliary treatment
- Serious adverse events
- Quality of life
- Time to stone clearance

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Search methods for identification of studies

We will perform a comprehensive search with no restrictions on the language of publication or publication status. We plan to rerun searches within three months prior to anticipated publication of the review.

Electronic searches

We will search the following sources from inception of each database (Appendix 1).

- Cochrane Library via Wiley
  - *Cochrane Database of Systematic Reviews* (CDSR)
  - Cochrane Central Register of Controlled Trials (CENTRAL)
  - Database of Abstracts of Reviews of Effects (DARE)
  - Health Technology Assessment Database (HTA)
- MEDLINE via PubMed (from 1946)
- EMBASE via Elsevier (from 1974)

We will also search the following.

- ClinicalTrials.gov (www.clinicaltrials.gov).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (apps.who.int/trialsearch).
- Grey literature repository from the current Grey Literature Report (www.greylit.org)

If we detect additional relevant key words during any of the electronic or other searches, we will modify the electronic search strategies to incorporate these terms and document the changes.

Searching other resources

We will try to identify other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included trials, reviews, meta-analyses and health technology assessment reports. We will also contact study authors of included trials to identify any further studies that we may have missed. We will contact drug/device manufacturers for ongoing or unpublished trials. We will search abstract proceedings of relevant meetings, specifically those of the American Urological Association, the European Association of Urology and the Endourological Society for the last three years (2016 to 2018) for unpublished studies.

Data collection and analysis

Selection of studies

We will use the reference management software EndNote to identify and remove potential duplicate records. Two review authors (MO, RV or NS) will independently scan the abstract, title, or both, of remaining records retrieved, to determine which studies should be assessed further, using Covidence software. Two review authors (MO, RV or NS) will investigate all potentially relevant records as full text, map records to studies, and classify studies as included studies, excluded studies, studies awaiting classification, or ongoing studies in accordance with the criteria for each provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We will resolve any discrepancies through consensus or recourse to a third review author (PD). If resolution of a disagreement is not possible, we will designate the study as 'awaiting classification' and we will contact study authors for clarification. We will document reasons for exclusion of studies that may have reasonably been expected to be included in the review in a 'Characteristics of excluded studies' table. We will present an adapted PRISMA flow diagram showing the process of study selection (Liberati 2009).

Data extraction and management

We will develop a dedicated data abstraction form that we will pilot test ahead of time.

For studies that fulfil inclusion criteria, two review authors (MO, RV or NS) will independently abstract the following information, which we will provide in the 'Characteristics of included studies' table.

- Study design
- Study dates (if dates are not available then we will report as such)
- Study settings and country
- Type of lithotripter device used and target size for stone fragments
- Participant inclusion and exclusion criteria (i.e. stone size, stone location)
- Participant details, baseline demographics (i.e. participant age, stone size, stone location, laterality)
- Procedure details (i.e. average number of shock waves administered, number of session)
- The number of participants by study and by study arm
- Details of relevant experimental and comparator interventions (i.e. type of alpha-blocker, dosage, duration of treatment in weeks)
- Definitions of relevant outcomes, and method and timing of outcome measurement as well as any relevant subgroups
- Imaging modality used to assess stone clearance (i.e. KUB radiograph, US, NCCT)
- Study funding sources
- Declarations of interest by primary investigators

We will extract outcome data relevant to this Cochrane Review as needed for calculation of summary statistics and measures of variance. For dichotomous outcomes, we will attempt to obtain numbers of events and totals for population of a 2 × 2 table, as well as summary statistics with corresponding measures of variance.

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For continuous outcomes, we will attempt to obtain means and standard deviations or data necessary to calculate this information. We will resolve any disagreements by discussion, or, if required, by consultation with a third review author (PD).
We will provide information, including trial identifier, about potentially relevant ongoing studies in the 'Characteristics of ongoing studies' table.
We will attempt to contact authors of included studies to obtain key missing data as needed.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents or multiple reports of a primary study, we will maximize yield of information by mapping all publications to unique studies and collating all available data. We will use the most complete data set aggregated across all known publications. In case of doubt, we will give priority to the publication reporting the longest follow-up associated with our primary or secondary outcomes.

Assessment of risk of bias in included studies

Three review authors (MO, RV, NS) will assess the risk of bias of each included study independently. We will resolve disagreements by consensus, or by consultation with a third review author (PD). We will assess risk of bias using Cochrane's 'Risk of bias' assessment tool (Higgins 2017). We will assess the following domains.

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other sources of bias

We will judge risk of bias domains as 'low risk', 'high risk' or 'unclear risk' and will evaluate individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We will present a 'Risk of bias' summary figure to illustrate these findings.
For performance bias (blinding of participants and personnel), we will consider all outcomes similarly susceptible to performance bias.
For detection bias (blinding of outcome assessment), we will group outcomes as susceptible to detection bias (investigator- or patient-assessed) or not susceptible to detection bias (objective).
We will define the following endpoints as investigator-assessed outcomes.

- Stone clearance
- Major adverse events
- Time to stone clearance

We will define the following endpoint as a patient-assessed outcome.

- Quality of life

We will define the following endpoint as an objective outcome:

- Auxiliary treatments

We will also assess attrition bias (incomplete outcome data) on an outcome-specific basis, and will present the judgement for each outcome separately when reporting our findings in the 'Risk of bias' tables.
We will further summarize the risk of bias across domains for each outcome in each included study, as well as across studies and domains for each outcome, in accordance with the approach for summary assessments of the risk of bias presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017).

Measures of treatment effect

We will express dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs). We will express continuous data as mean differences (MDs) with 95% CIs unless different studies use different measures to assess the same outcome, in which case we will express data as standardized mean differences with 95% CIs. We will express time-to-event data as hazard ratios (HRs) with 95% CIs.

Unit of analysis issues

The unit of analysis will be the individual participant. We plan to account for the level at which randomization occurred, for example cluster randomized trials. If we identify trials with more than two intervention groups for inclusion in the review, we will handle these in accordance with guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

Dealing with missing data

We will obtain missing data from study authors, if feasible, and will perform intention-to-treat (ITT) analyses if data should be available; we will otherwise perform available case analyses but identify the analysis as such. We will investigate attrition rates, e.g. dropouts, losses to follow-up and withdrawals, and will critically appraise issues of missing data. We will not impute missing data.

Assessment of heterogeneity

In the event of excessive heterogeneity unexplained by subgroup analyses, we will not report outcome results as the pooled effect estimate in a meta-analysis but will provide a narrative description of the results of each study.
We will identify heterogeneity (inconsistency) through visual inspection of the forest plots to assess the amount of overlap of CIs, and the I^2 statistic, which quantifies inconsistency across studies to assess the impact of heterogeneity on the meta-analysis (Higgins

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2002; Higgins 2003); we will interpret the I^2 statistic as follows (Deeks 2017).

- 0% to 40%: may not be important
- 30% to 60%: may indicate moderate heterogeneity
- 50% to 90%: may indicate substantial heterogeneity
- 75% to 100%: considerable heterogeneity

When we find heterogeneity, we will attempt to determine possible reasons for it by examining individual study and subgroup characteristics.

Assessment of reporting biases

We will attempt to obtain study protocols to assess for selective outcome reporting.

If we include 10 studies or more investigating a particular outcome, we will use funnel plots to assess small-study effects. Several explanations can be offered for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials) and publication bias. We will therefore interpret results carefully.

Data synthesis

Unless there is good evidence for homogeneous effects across studies, we will summarize data using a random-effects model. We will interpret random-effects meta-analyses with due consideration of the whole distribution of effects. In addition, we will perform statistical analyses according to the statistical guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). For dichotomous outcomes, we will use the Mantel-Haenszel method; for continuous outcomes, we will use the inverse variance method; and for time-to-event outcomes, we will use the generic inverse variance method. We will use Review Manager 5 software to perform analyses (Review Manager 2014).

Subgroup analysis and investigation of heterogeneity

We expect the following characteristics to introduce clinical heterogeneity, and plan to carry out subgroup analyses with investigation of interactions.

- Stone location (renal versus proximal ureter versus distal ureter)
- Stone size (< 1 cm vs ≥ 1 cm)
- Specific alpha-blocker (e.g. terazosin versus doxazosin)
- Type of lithotripter (HM3 versus others)

The planned subgroup analyses by stone location, size and type of alpha-blocker are based on observations of potential subgroup effects demonstrated in previous studies for the use of MET for ureteral colic (Campschroer 2018; Hollingsworth 2016; Preminger 2007). The planned subgroup analysis based on type of lithotripter is based on the fact that different shockwave lithotripter devices vary in their effectiveness in stone fragmentation with the HM3 lithotripter (as first generation lithotripter with the largest acoustic energy focal zone) being the most powerful in achieving stone fragmentation (McClain 2013).

We will use the test for subgroup differences in Review Manager 5 to compare subgroup analyses if there are sufficient studies (Review Manager 2014). We plan to limit subgroup analyses to primary outcomes only.

Sensitivity analysis

We plan to perform sensitivity analyses, limited to the primary outcomes, in order to explore the influence of the following factors (when applicable) on effect sizes.

- Restricting the analysis by taking into account risk of bias, by excluding studies at 'high risk' or 'unclear risk'.
- Limiting the analysis to studies with a documented single SWL session and studies with multiple SWL sessions that reported outcomes separately by the number of sessions (thereby allowing us to focus on the results of a single session only).

'Summary of findings' table

We will present the overall quality of the evidence for each outcome according to the GRADE approach, which takes into account five criteria not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias), but also to external validity, such as directness of results (Guyatt 2008). For each comparison, two review authors (MO, RV or NS) will independently rate the quality of evidence for each outcome as 'high', 'moderate', 'low', or 'very low' using GRADEpro GDT. We will resolve any discrepancies by consensus or, if needed, by arbitration by a third review author (PD). For each comparison, we will present a summary of the evidence for the main outcomes in a 'Summary of findings' table, which provides key information about the best estimate of the magnitude of the effect in relative terms and absolute differences for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and the rating of the overall confidence in effect estimates for each outcome (Guyatt 2011; Schünemann 2017). If meta-analysis is not possible, we will present results in a narrative 'Summary of findings' table.

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* *Indicates the major publication for the study*

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APPENDICES

Appendix 1. Search strategy

Database	Search terms
MEDLINE (via PubMed)	1. shockwave lithotripsy[tw] OR SWL[tiab] 2. extracorporeal shockwave lithotripsy[tw] OR ESWL[tiab] 3. 1 OR 2 4. Adrenergic alpha-Antagonists[mh] OR adrenergic alpha-Antagonists[tiab] 5. Alfuzosin[Supplementary Concept] OR alfuzosin[tiab] 6. Doxazosin[mh] OR doxazosin[tiab] 7. Terazosin[Supplementary Concept] OR terazosin[tiab] 8. Tamsulosin[mh] OR tamsulosin[tiab] 9. Silodosin[Supplementary Concept] OR silodosin[tiab] 10. Naftopidil[Supplementary Concept] OR naftopidil[tiab] 11. 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 12. 3 AND 11
Embase (via Elsevier)	1. 'shockwave lithotripsy'/exp 2. extracorporeal AND lithotripsy 3. SWL OR ESWL 4. 1 OR 2 OR 3 5. 'alpha adrenergic receptor blocking agent'/exp 6. 'alfuzosin'/exp OR 'doxazosin'/exp OR' terazosin'/exp OR 'tamsulosin'/exp OR 'silodosin'exp OR 'naftopidil'/exp 7. 5 or 6 8. 4 and 7
Cochrane Library	1. shockwave lithotripsy 2. extracorporeal shockwave lithotripsy 3. #1 OR #2 4. adrenergic alpha-antagonists 5. alfuzosin 6. doxazosin 7. terazosin 8. tamsulosin 9. silodosin 10. naftopidil 11. #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 12. #1 AND #3
ClinicalTrials.gov and ICTRP	1. Extracorporeal shockwave lithotripsy AND adrenergic alpha-antagonists

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CONTRIBUTIONS OF AUTHORS

Makinna Oestreich (MO): wrote the protocol.

Niranjan Sathianathen (NS): wrote the protocol.

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Robin Vernooij (RV): wrote the protocol.

Gretchen Kuntz (GK): wrote the protocol, developed search strategy.

Charles Scales (CS): wrote the protocol.

Philipp Dahm (PD): wrote the protocol.

DECLARATIONS OF INTEREST

MO: none known.

NS: none known.

EH: none known.

RV: none known.

GK: none known.

CS: none known.

PD: none known.

SOURCES OF SUPPORT

Internal sources

- Department of Urology, University of Minnesota, Minneapolis, MN, USA.
- Minneapolis Veterans Administration Health Care System, Minneapolis, MN, USA.

External sources

- No sources of support supplied

NOTES

We have based parts of the Methods section of this protocol on a standard template developed by the Cochrane Metabolic and Endocrine Disorders Group, which has been modified and adapted for use by the Cochrane Urology Group.

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