Comparison of efficacy of various drugs used for medical expulsive therapy for distal ureter stones: a systematic review and network meta-analysis.

Gopal Sharma[1], Pawan Kaundal[1], Tarun Pareek[1], Shantanu Tyagi[1], Aditya Sharma[1], and Sudheer Devana[1]

[1]PGIMER

April 28, 2020

Abstract

Aim: Medical expulsive therapy for ureteric stones incudes various drug interventions. For lower ureteric stone which individual drug treatment or combination is best as MET is not known. Aim of this study was to compare efficacy of various drug treatments for distal ureter stones. Methods: Systematic literature search was conducted to include all the randomized study comparing various drug interventions for lower ureter stones. Standard Preferred reporting Items for systematic review and meta-analysis for network meta-analysis (PRISMA-NMA) were pursued. RESULTS: In this review, 50 randomized studies with 12,382 patients were included. For stone expulsion rate (SER), compared to placebo all the treatment groups were more effective except nifedipine and sildenafil. According to the SUCRA values obtained naftopidil plus steroid was the highest rank and nifedipine lowest. For stone expulsion time (SET), compared to placebo only tadalafil plus silodosin, nifedipineplus steroid,alfuzosin,silodosin, tadalafil and tamsulosin were more effective. SUCRA values were highest for tadalafil plus silodosin and least for naftopidil plus steroid. From subgroup analysis with individual drugs for SER, SUCRA values were highest for naftopidil followed by silodosin and SET was highest for silodosin and least for naftopidil. Conlcusion: For lower ureter stone, tadalafil plus silodosin is the best combination and silodosin best individual drug considering the SET and SER. Nifedipine as montherapy is no more effective than control group.

Introduction

Urolithiaisis is a fairly common condition and can be source of substantial morbidity and economic burden[1, 2]. Ureteric colics secondary to ureteric stone can be source of agonizing pain and multiple emergency visits. Lower ureter is the most common site of lodgement of stone and accounts for about 50% of stones requiring surgical interventions[3]. Spontaneous passage of stones in the lower ureter is seen in about 70% and 50% of the patients with stones size [?]5mm and 5-10 mm[4, 5]. Thus not all lower ureteric stones may need surgical intervention unless causing recurrent colics. Greatest benefit of MET has been found in patients with stone size >5mm as stones below this size have high chances of spontaneous expulsion[6].

Treatment options for management of ureteric stones include medical expulsive therapy (MET), shockwave lithotripsy (SWL) and ureteroscopic lithotripsy (URSL). Shockwave lithotripsy and surgical procedures like URSL are not free of complication thus alternative conservative methods have been applied especially when stones are located n distal ureter and are less than 10 mm. Multiple drugs such as α-blockers (tamsulosin, silodosin, alfuzosin and naftopidil)[7-9], nifedipine (calcium channel blockers (CCB's))[10] and phosphodiesterase inhibitors (PDEI) (sildenafil[11] and tadalafil[12]) have been found to be effective in facilitating ureter stones compared to general measures such as use of non-steroidal inflammatory drugs (NSAIDS), hydration, anti-spasmodics, diuretics and placebo. Of these drugs tamsulosin has been widely studied and has been found to facilitate stone expulsion not only in distal as well as other parts of ureter. Efficacy of α-blockers as MET

is well established for all parts of the ureter however data on use of other class of drugs is still immature and recent[9, 13, 14]. Further, various combinations such as α-blockers with PDEI-α-blockers[15, 16] with NSAIDS[17] and steroids[18-22] have been tried and have found variable success as compared to these drugs alone.

The primary objective of this study was to systematically review all the available literature regarding various drugs used for MET (PDEI, α-blockers and CCB's) for the treatment of distal ureter stones and generate evidence for best available drug or combination.

Materials and Methods

This systematic review and network meta-analysis was performed with frequentist approach[23]and standard Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines for conducting network meta-analysis (NMA) were followed[24].

Literature search

An exhaustive literature search for various electronic databases such as PubMed/Medline, Scopus, Embase, CENTRAL and web of science was conducted by two study (GS & PK) authors independently. Literature search was conducted from time of inception of these databases till March 2020. Literature search was limited to English language only. Search string used for literature search was based on Patient, Intervention, Control and Outcome (PICO) guidelines. Following keywords and strategy were used:

Patient : Lower ureteric stone OR Lower ureteric calculi OR Distal ureteric stone OR Distal ureteric calculi.

Intervention: alfuzosin OR silodosin OR tamsulosin OR naftopidil OR alfa-blockers OR phosphodiesterase inhibitors OR tadalafil OR sildenafil OR nifedipine

Control : No treatment OR control OR placebo

Outcome: Stone expulsion

The search results thus obtained from various databases search was transferred on to a citation manager and duplicates were removed. Additional articles were also sought from various review articles on same topic and hand searches of references selected for full-text review was also undertaken. Search strategy used for PubMed has been provided in supplementary file (S1)

Study eligibility criteria

Following comprehensive literature search, initial title and abstract screening was conducted by two study authors independently to screen articles for possible inclusion into the study based on below mentioned exclusion and inclusion criteria.

Inclusion

1. Study should contain data on number of stone expulsion or time to stone expulsion in adult patients with lower ureteric stones with use of any of the four commonly used alfa-blockers, PDEI, nifedipine (CCB) alone or in combination. Comparison could be against control group, placebo or with each other.
2. Only randomized control trials will be included in this review.

Exclusion

1. Non-randomized studies
2. Case reports, editorials, letters and reviews.
3. Studies in pediatric age group (age< 18 years) will be excluded.
4. Not containing data on stone expulsion rate at the completion of study.
5. Use of uncommonly used drugs such as terazosin, doxazosin and anticholinergics

Studies were then selected for full-text review following initial title and abstract screening. Full-text review was then performed and studies satisfying inclusion and exclusion criteria were included in review. At any point of discrepancy between two study authors arbitration with other study authors was done (ST & TP).

Data extraction

Two study authors (PK & TP) independently extracted data from the included studies on a pre-determined format including following variables such as First author, year, type of study, country, type of treatment, duration of treatment, baseline comparability according to age, sex, stone size, stone expulsion rate and time to stone expulsion. Discrepancy of data was resolved after arbitration with other study authors (GS & ST).

Outcome

Primary outcome studied was stone expulsion rate at the end of study period in the treatment and the control group. We also provided data for ranking various drugs on their efficacy for expulsion of distal ureteric stones in terms of stone expulsion rate (secondary outcome). Data on time to stone expulsion was also analyzed in this study and various drugs were ranked accordingly.

Statistical analysis and certainty of evidence

Please see supplementary table file for details.

Results

Literature search and study characteristics

Literature search of various databases yielded a total of 360 citations which were imported on a citation manager. Of these 107 duplicate articles were removed and other 178 articles were removed after initial title and abstract screening due to various reasons (Figure 1). Seventy-five articles were selected for full text review. For final analysis 50 articles were included and remaining 25 articles were excluded due to non randomized nature of studies.

Study characteristics

In this review a total of 50 RCT's with 12382 patients were included[6, 11, 15, 19, 22, 25-68]. Multiple treatments across these studies were assessed for medical expulsion of lower ureteric stone (alfuzosin (AL), alfuzosin plus steroids (AL-S), naftopidil (NAF), naftopidil plus steroids (NAF-S), nifedipine (NIF), nifedipine plus steroids (NIF-S), sildenafil (SIL), silodosin (SILO), tadalafil (TAD), tamsulosin (TAM), tamsulosin plus steroids (TAM-S), tadalafi plus silodosin, (TADplusSILO), tadalafil plus tamsulosin (TADplusTAM), tadalafil plus tamsulosin plus steroids (TADplusTAM-S). Control group was variably defined across the studies some including placebo (16 studies), others including best medical management with adequate hydration, analgesics and anti-spasmodics. Control with no specific treatment group was found in 9 studies[26, 33, 45, 46, 53, 58, 59, 65, 69], diclofenac was used as control in 5 studies[6, 27, 47-49], study by Cervanakov[28] used tramadol with Veral and diazepam and Sio et al used Aescin with diclofenac[70]. Duration of treatment was variable across the studies ranging from 10 days to 6 weeks. All the groups compared well for baseline characteristics such as age, sex and stone size. All the studies included patients with stone size less than 10 mm. (Table 1)

Network map for the two outcomes i.e. stone expulsion rate (SER) and stone expulsion time (SET) are provided in Figure 2. For SER mixed evidence was available for 27 comparisons whereas indirect evidence was available for 78 comparisons. Most common comparison studied for this outcome was TAM versus C with 21 studies followed by NIF vs. TAM (6 studies), ALvs.C (5 studies), AL vs. TAM (4 studies). Tamsulosin was the most commonly studied drug across the network for SER with representation in 34 studies whereas AL-S[71], TADplusTAM[42], TADplusTAM-S[43], TADplusSILO[15] and SIL[11] were limited to single studies. For secondary outcome i.e. SET, data was available from 32 studies with 13 treatment groups AL, NAF-S, NIF, NAF, NIF-S SIL, SILO, TAD, TADplusSILO, TADplusTAM, TADplusTAM-S, TAM-S and TAM. Most

common comparison across the studies was C vs. TAM (13 studies), followed by 3 comparisons for each AL vs. C, C vs. NAF, SILO vs. TAM and TAM vs. TAD.

Stone expulsion rate (SER)

Compared to placebo all the treatment groups were more effective except NIF AND SIL (figure 3). Risk ratio (RR) of stone expulsion rate compared to placebo were highest for NAF-S [2.4 (1.6, 3.8)] followed by TADplusTAM-S [2.1 (1.3, 3.6)] and TADplusSILO [1.9 (1.3, 2.8)]. Rest of the risk ratios with their 95% confidence intervals (CI) have been provided in the table 2. SUCRA values were calculated to estimate the rank of efficacy according to stone expulsion rate (Supplementary Table 2). According to the SUCRA values obtained NAF-S had the highest rank followed by TADplusTAM-S and TADplusSILO. NIF had the lowest sucra value among treatment modalities.Global approaches for inconsistency models revealed consistency assumption for direct and indirect assumptions. Loop specific approach revealed 13 treatment loops without inconsistency (Supplementary figure 2). Node splitting revealed inconsistency for three comparisons i.e. C vs NAF, C vs. SILO and NAF vs. TAM.

Stone expulsion time (SET)

Compared to placebo only TADplusSILO, NIF-S, AL, SILO, TAD and TAM were more effective (Figure 3). Standard Mean differences (SMD) for stone expulsion time compared to placebo were best for TADplusSILO (SMD -2.8 (-4.3, -1.2) followed by NIF-S (SMD -2.0 (-3.2, -0.8) and SILO (SMD -1.4 (-2.1, -0.6) (Supplementary Table 3). SUCRA values obtained for time to stone expulsion estimate revealed highest values for TADplusSILO and least for NAF-S. (Supplementary Table 4 and Supplementary figure 4). Global test for inconsistency and node splitting approach did not reveal inconsistency in any comparisons. Loop specific approach revealed inconsistency in AL-C-NIF and SILO-TADplusSILO-TAM loops (Supplementary figure 5).

Subgroup analysis

We also performed subgroup analysis to test the efficacy of individual drug treatments i.e AL, NAF, NIF, SIL, SILO, TAD, TAM. For SER there were 43 studies for these 7 comparisons and highest sucra values were obtained for NAF followed by SILO and TAD and least for NIF. For similar group, for SET with 27 studies and 7 comparisons, highest sucra values were obtained for SILO followed by SIL and TAD and least for NAF (supplementary table 5 and 6).

We also plotted cluster ranking plots for this network analysis presenting jointly the relative ranking of treatments (based on SUCRA percentages) for SER and SET (Figure 4A). Treatments occupying the upper right corner of this plot perform well for both the outcomes. Such as tadalafil and silodosin combination for the whole network and silodosin for the individual drug treatment analysis. (Figure 4A and 4B)

Sensitivity analysis

Sensitivity analysis was performed according to studies with placebo as control group and studies not at high risk of bias for primary outcome i.e. SER and results were consistent with the previously obtained results.

Certainty of evidence

Risk of bias assessment as performed by study authors revealed 20 studies at high risk of bias, 10 at unclear risk of bias and 20 at low risk of bias. Most of the studies lacked placebo groups thus were at high risk of performance bias furthermore allocation to treatment groups was not blinded in many studies. None of the studies were at risk of attrition or reporting bias. Supplementary figure 3 depicts bar charts showing contribution of each study to the network estimate. Overall there were 27 mixed evidence and 78 indirect evidences and quality of evidence was ranked from very low to high and has been provided in supplementary table for primary outcome i.e. SER. Funnel plots showed mild asymmetry for the outcome SER however on regression analysis it was not significant furthermore funnel plot for SET was symmetrical (Supplementary figure 5 and 6)

Discussion

Choice of treatment for ureteral stones not only depends on stone-related factors such as size, location and density but also depends upon patient's symptoms and comorbidities. Despite numerous technological advances in the minimally invasive treatment modalities such as URSL and SWL, there are inherent risks which cannot be completely eliminated. Therefore for non-urgent, asymptomatic, small and especially distal ureteric stones attempt of conservative treatment or MET seems logical. The primary aim of MET is not only to facilitate expulsion of stones along the length of the ureter but also reduce the chances of obstruction, ureteric colics, need for hospitalizations and surgical procedures. Alfa-blockers are an established therapy for stone expulsion. Alfa-receptors are found throughout the length of ureter, density is particularly high in distal ureters. Many studies have also found α_{1D} receptors in high density in distal ureter[72-74]. In a network meta-analysis by Sridharan et al[75] comparing all the alfa-blockers for ureteral stones, authors noted SER to be best with terazosin and SET to be best with silodosin and authors of the study concluded silodosin of be the best alfa-blocker. Other groups of drugs such as Calcium channel blockers and PDEI have also found success as MET, whereas role of other drugs such as NSAIDS[76, 77] and corticosteroids is controversial. Distal ureter stones present unique atmosphere to the drug therapies due to rich receptor density and short distance to be traversed along the length of ureter to bladder and more often than not such stones if asysmptomatic are subjected MET. Thus aim of this study was to compare the efficacy of three commonly used of drug groups i.e. alfa-blockers, CCB's and PDEI for distal ureteric stones as medical expulsive therapy.

In this large network meta-analysis with 50 RCT's and 12,382 patients, both direct and indirect evidence was sought to compare the efficacy of above mentioned group of drugs in terms of SER and SET. For the primary outcome i.e. SER there were 14 treatment groups and data was available from all the 50 RCT's and we found NAF-S followed by TADplusTAM-S, TADplusSILO and TAM-S were the best treatments and nifedipine the worst. Furthermore, in our subgroup analysis of individual drugs, we noted naftopidil to be the highest ranked and nifedipine lowest ranked. We also noted that apart from nifedipine and sildenafil all the treatment groups were more effective than control group for stone expulsion. Our results are in line with previously performed network meta-analysis[78] for ureteral stones (irrespective of site) by Liu et al, they also found NAF-S to be the best treatment group followed by tadalafil plus silodosin. High density of α_{1D} in the lower ureter could explain the efficacy of naftopidil in the present study. Nifedipine has been studied in a large RCT by Pickard et al[51] and was found to be no more effective than placebo irrespective of stone size and location. Nifedipine has been compared to tamsulosin in a previously conducted meta-analysis by Wang et al[10] and was found to be less efficacious than tamsulosin in terms of SER and SET. Finally, Amer et al[79] in a systematic review concluded that CCB's are no more effective than control group for SER and SET. Thus our results establish naftopidil plus steroids as the best treatment, naftopidil as best individual treatment and nifedipine as the worst treatment modality for lower ureteric stones.

For stone expulsion time, results in this review were derived from 32 studies including 6417 patients and found TADplusSILO followed by NIF-S and SILO to be highest ranked for SET and NAF-S to be the worst. In the previous meta-analysis by Liu et al[78], tadalafil plus silodosin was the best followed by tamsulosin plus tadalafil and corticosteroids, tamsulosin plus steroids for SET. Their analysis did not contain nifedipine plus steroid group, also nifedipine and antispasmodics were the worst. From data on individual drugs in this study, silodosin was highest ranked and naftopidil worst. Silodosin has been noted for rapid onset of action for patients with benign prostatic enlargement with lower urinary tract symptoms in phase III trials[80]. With silodosin improvent in urine flow is noted within 2-6 hours of drug administration[80]. Thus corollary to effect in BPH patients its effect on SER and SET can be attributed to rapid onset of action and selective α_{1A}antagonistic properties. In a review by Sridharan et al[75], authors concluded that silodosin may be the best alfa-blockers for MET. Considering the data available from individual drug treatment subgroup where best treatment for SER was naftopidil followed by silodosin and for SET silodosin was highest ranked and naftopidil lowest ranked. Thus individual drug subgroup data from this study suggests that silodosin may be the best drug among other alfa-blockers, PDEI and CCB's. Before suggesting silodosin as the best dug for MET we must admit two important limitations. First, this study lacked comparison of silodosin to older alfa-blockers such as terazosin and doxazosin. We excluded them from this review as they are not commonly

in use. Secondly, side effect profile of each drug treatment was not considered in this study. Retrograde ejaculation is a fairly common complications seen with silodosin and may be of concern younger patients.

Limitations

There are several limitations in this study; firstly out of 50 studies included in this studies 20 were at high risk of bias contributing to overall low quality of evidence. Evidence generated from this review ranged from very low to high for various comparisons. In this study, there were a total of 105 comparisons of which 27 were direct and 78 indirect. Using CINeMA approach 36 comparisons were Very Low, 46 were Low, 18 were moderate and only 5 were rated as high. Another important limitation of this study is that the control group was variably defined across different studies and only 16 trials were placebo controlled. Dose of various active drug treatments were also variable for some drugs such as in the study by Lv et al[17] authors used naftopidil in 50mg once a day dose, in the study by Zhou et al[65] 10 mg once a day was used and Kumar et al[45] used 75 mg once a day dose. Also, we amalgamated all the corticosteroids used as adjunctive with various drugs one group i.e. steroids. There was significant inconsistency in the network analysis used for primary outcome SER using global and node splitting approaches. However, we performed sensitivity analysis according to studies at low or unclear risk of bias and studies with placebo group as control for SER and did not find much difference compared to the original network. We also did not assess the side effect profile of each of the drug as primary aim of this review was to assess the efficacy. From methodology point of view we included studies limited to English language and excluded conference abstracts. We acknowledge that conference abstracts are an important source of grey literature but we also understand that they are not peer reviewed and lack data in various domains. Certain studies on drug treatments such as terazosin, doxazosin and anticholinergics were excluded as these are not commonly used for this indication. Finally, we acknowledge the inherent limitations of the frequentist approach used for this network meta-analysis[81].

Conclusion

In this network meta-analysis of 50 studies with 14 drug treatment groups for stone expulsion rate we noted naftopidil plus steroid to be the best and nifedipine the worst. For individual drug comparison we noted naftopidil followed by silodosin was the best and nifedipine the worst. For secondary outcome stone expulsion time, tadalafil plus silodosin was the best and naftopidil plus steroids the worst. From individual drug comparison we noted silodosin to be best and naftopidil worst. Considering both the efficacy parameters Silodosin appears to the best individual treatment modality with best expulsion time and second best expulsion rate for lower ureter stones less than 10 mm.

REFERENCES

1. Johnson CM, Wilson DM, O'Fallon WM, Malek RS, Kurland LT. Renal stone epidemiology: a 25-year study in Rochester, Minnesota. Kidney Int. 1979;16:624-31.

2. Stamatelou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC. Time trends in reported prevalence of kidney stones in the United States: 1976-1994. Kidney Int. 2003;63:1817-23.

3. El-Barky E, Ali Y, Sahsah M, Terra AA, Kehinde EO. Site of impaction of ureteric calculi requiring surgical intervention. Urolithiasis. 2014;42:67-73.

4. Preminger GM, Tiselius HG, Assimos DG, Alken P, Buck AC, Gallucci M, et al. 2007 Guideline for the management of ureteral calculi. Eur Urol. 2007;52:1610-31.

5. Smith RD, Shah M, Patel A. Recent advances in management of ureteral calculi. F1000 Med Rep. 2009;1.

6. Aldemir M, Ucgul YE, Kayigil O. Evaluation of the efficiency of tamsulosin and Rowatinex in patients with distal ureteral stones: a prospective, randomized, controlled study. Int Urol Nephrol. 2011;43:79-83. Epub 2010/06/11. eng.

7. Hsu YP, Hsu CW, Bai CH, Cheng SW, Chen KC, Chen C. Silodosin versus tamsulosin for medical expulsive treatment of ureteral stones: A systematic review and meta-analysis. PLoS ONE. 2018;13. English.

8. Campschroer T, Zhu X, Vernooij RWM, Lock MTWT. Alpha-blockers as medical expulsive therapy for ureteral stones. Cochrane Database of Systematic Reviews. 2018;2018. English.

9. Aboumarzouk OM, Jones P, Amer T, Kotsiris D, Emiliani E, Somani B, et al. What Is the Role of α-Blockers for Medical Expulsive Therapy? Results From a Meta-analysis of 60 Randomized Trials and Over 9500 Patients. Urology. 2018;119:5-16. English.

10. Wang H, Man LB, Huang GL, Li GZ, Wang JW. Comparative efficacy of tamsulosin versus nifedipine for distal ureteral calculi: a meta-analysis. Drug Des Devel Ther. 2016;10:1257-65. Epub 2016/04/22. eng.

11. Shokeir AA, Tharwat MA, Abolazm AE, Harraz A. Sildenafil citrate as a medical expulsive therapy for distal ureteric stones: A randomised double-blind placebo-controlled study. Arab J Urol. 2016;14:1-6. Epub 2016/03/12. eng.

12. Bai Y, Yang Y, Wang X, Tang Y, Han P, Wang J. Tadalafil Facilitates the Distal Ureteral Stone Expulsion: A Meta-Analysis. J Endourol. 2017;31:557-63. Epub 2017/04/07. eng.

13. Hollingsworth JM, Canales BK, Rogers MA, Sukumar S, Yan P, Kuntz GM, et al. Alpha blockers for treatment of ureteric stones: systematic review and meta-analysis. BMJ. 2016;355:i6112.

14. Campschroer T, Zhu X, Vernooij RWM, Lock T. alpha-blockers as medical expulsive therapy for ureteric stones: a Cochrane systematic review. BJU Int. 2018;122:932-45.

15. Rahman MJ, Faridi MS, Mibang N, Singh RS. Comparing tamsulosin, silodosin versus silodosin plus tadalafil as medical expulsive therapy for lower ureteric stones: A randomised trial. Arab J Urol. 2018;16:245-9. Epub 2018/06/13. eng.

16. Kumar S, Jayant K, Agrawal S, Singh SK. Comparative efficacy of tamsulosin versus tamsulosin with tadalafil in combination with prednisolone for the medical expulsive therapy of lower ureteric stones: a randomized trial. Korean J Urol. 2014;55:196-200.

17. Lv JL, Tang QL. Comparative evaluation of efficacy of use of naftopidil and/or celecoxib for medical treatment of distal ureteral stones. Urolithiasis. 2014;42:541-7. Epub 2014/08/21. eng.

18. Porpiglia F, Vaccino D, Billia M, Renard J, Cracco C, Ghignone G, et al. Corticosteroids and tamsulosin in the medical expulsive therapy for symptomatic distal ureter stones: single drug or association? Eur Urol. 2006;50:339-44. Epub 2006/04/01. eng.

19. Dellabella M, Milanese G, Muzzonigro G. Randomized trial of the efficacy of tamsulosin, nifedipine and phloroglucinol in medical expulsive therapy for distal ureteral calculi. J Urol. 2005;174:167-72. Epub 2005/06/11. eng.

20. Hwang EC, Hwang IS, Yu HS, Kim SO, Jung SI, Kang TW, et al. Effects of alfuzosin with methylprednisolone for spontaneous expulsion and pain control of lower ureteral stone. Urol Res. 2012;40:605-9. Epub 2012/05/25. eng.

21. Saita A, Bonaccorsi A, Marchese F, Condorelli SV, Motta M. Our experience with nifedipine and prednisolone as expulsive therapy for ureteral stones. Urol Int. 2004;72 Suppl 1:43-5.

22. Borghi L, Meschi T, Amato F, Novarini A, Giannini A, Quarantelli C, et al. Nifedipine and methylprednisolone in facilitating ureteral stone passage: a randomized, double-blind, placebo-controlled study. J Urol. 1994;152:1095-8.

23. Shim S, Yoon BH, Shin IS, Bae JM. Network meta-analysis: application and practice using Stata. Epidemiol Health. 2017;39:e2017047.

24. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162:777-84.

25. Al-Ansari A, Al-Naimi A, Alobaidy A, Assadiq K, Azmi MD, Shokeir AA. Efficacy of tamsulosin in the management of lower ureteral stones: a randomized double-blind placebo-controlled study of 100 patients. Urology. 2010;75:4-7. Epub 2010/01/30. eng.

26. Alizadeh M, Magsudi M. The effect of tamsulosin in the medical treatment of distal ureteral stones. Glob J Health Sci. 2014;6:44-8. Epub 2014/11/05. eng.

27. Bajwa MSA, Rahim J, Rahim J, Saeed Q, Hussain K, Ashraf S, et al. Efficacy of tamsulosin for clearance of lower ureteric stones. Pakistan journal of medical and health sciences. 2013;7:769-72.

28. Cervenakov I, Fillo J, Mardiak J, Kopecny M, Smirala J, Lepies P. Speedy elimination of ureterolithiasis in lower part of ureters with the alpha 1-blocker–Tamsulosin. Int Urol Nephrol. 2002;34:25-9.

29. El-Gamal O, El-Bendary M, Ragab M, Rasheed M. Role of combined use of potassium citrate and tamsulosin in the management of uric acid distal ureteral calculi. Urol Res. 2012;40:219-24. Epub 2011/08/23. eng.

30. Elgalaly H, Eliwa A, Seleem M, Salem E, Omran M, Shello H, et al. Silodosin in the treatment of distal ureteric stones in children: a prospective, randomised, placebo-controlled study. Arab journal of urology. 2017;15:194-8.

31. Elgalaly H, Sakr A, Fawzi A, Salem EA, Desoky E, Shahin A, et al. Silodosin vs tamsulosin in the management of distal ureteric stones: a prospective randomised study. Arab journal of urology. 2016;14:12-7.

32. Vincendeau S, Bellissant E, Houlgatte A, Dore B, Bruyere F, Renault A, et al. Tamsulosin hydrochloride vs placebo for management of distal ureteral stones: a multicentric, randomized, double-blind trial. Arch Intern Med. 2010;170:2021-7. Epub 2010/12/15. eng.

33. Yilmaz E, Batislam E, Basar MM, Tuglu D, Ferhat M, Basar H. The comparison and efficacy of 3 different alpha1-adrenergic blockers for distal ureteral stones. J Urol. 2005;173:2010-2. Epub 2005/05/10. eng.

34. Agrawal M, Gupta M, Gupta A, Agrawal A, Sarkari A, Lavania P. Prospective randomized trial comparing efficacy of alfuzosin and tamsulosin in management of lower ureteral stones. Urology. 2009;73:706-9. Epub 2009/02/06. eng.

35. Ahmad H, Azim W, Akmal M, Murtaza B, Mahmood A, Nadim A, et al. MEDICAL EXPULSIVE TREATMENT OF DISTAL URETERAL STONE USING TAMSULOSIN. J Ayub Med Coll Abbottabad. 2015;27:48-50. Epub 2015/07/18. eng.

36. Cha WH, Choi JD, Kim KH, Seo YJ, Lee K. Comparison and efficacy of low-dose and standard-dose tamsulosin and alfuzosin in medical expulsive therapy for lower ureteral calculi: prospective, randomized, comparative study. Korean J Urol. 2012;53:349-54. Epub 2012/06/07. eng.

37. Dell'Atti L. Silodosin versus tamsulosin as medical expulsive therapy for distal ureteral stones: a prospective randomized study. Urologia. 2015;82:54-7. Epub 2014/09/10. eng.

38. Furyk JS, Chu K, Banks C, Greenslade J, Keijzers G, Thom O, et al. Distal Ureteric Stones and Tamsulosin: A Double-Blind, Placebo-Controlled, Randomized, Multicenter Trial. Ann Emerg Med. 2016;67:86-95.e2. Epub 2015/07/22. eng.

39. Ochoa-Gomez R, Prieto-Diaz-Chavez E, Trujillo-Hernandez B, Vasquez C. Tamsulosin does not have greater efficacy than conventional treatment for distal ureteral stone expulsion in Mexican patients. Urol Res. 2011;39:491-5. Epub 2011/04/26. eng.

40. Hermanns T, Sauermann P, Rufibach K, Frauenfelder T, Sulser T, Strebel RT. Is there a role for tamsulosin in the treatment of distal ureteral stones of 7 mm or less? Results of a randomised, double-blind, placebo-controlled trial. Eur Urol. 2009;56:407-12. Epub 2009/04/21. eng.

41. Itoh Y, Okada A, Yasui T, Hamamoto S, Hirose M, Kojima Y, et al. Efficacy of selective alpha1A adrenoceptor antagonist silodosin in the medical expulsive therapy for ureteral stones. International journal of urology. 2011;18:672-4.

42. Jayant K, Agrawal R, Agrawal S. Tamsulosin versus tamsulosin plus tadalafil as medical expulsive therapy for lower ureteric stones: a randomized controlled trial. Int J Urol. 2014;21:1012-5. Epub 2014/06/05. eng.

43. Kumar S, Jayant K, Agrawa S, Singh SK. Comparative efficacy of tamsulosin versus tamsulosin with tadalafil in combination with prednisolone for the medical expulsive therapy of lower ureteric stones: a randomized trial. Korean journal of urology. 2014;55:196-200.

44. Doherty R, Manley K, Bultitude M, Gordon S, Irving S, Kumar S, et al. Extracorporeal shockwave lithotripsy-a multicentre UK snapshot study. BJU international Conference: 71st annual scientific meeting of the british association of urological surgeons, BAUS 2015 United kingdom. 2015;115:17.

45. Kumar S, Kurdia KC, Ganesamoni R, Singh SK, Nanjappa B. Randomized controlled trial to compare the safety and efficacy of naftopidil and tamsulosin as medical expulsive therapy in combination with prednisolone for distal ureteral stones. Korean journal of urology. 2013;54:311-5.

46. Sameer S, Lal S, Charak K, Chakravarti S, Kohli S, Ahmad S. Efficacy of nifedipine and alfuzosin in the management of distal ureteric stones: a randomized, controlled study. Indian journal of urology. 2014;30:387-91.

47. Ahmed AF, Al-Sayed AY. Tamsulosin versus Alfuzosin in the Treatment of Patients with Distal Ureteral Stones: Prospective, Randomized, Comparative Study. Korean J Urol. 2010;51:193-7. Epub 2010/04/24. eng.

48. El Said NO, El Wakeel L, Kamal KM, Morad A. Alfuzosin Treatment Improves The Rate and Time for Stone Expulsion in Patients with Distal Uretral Stones: A Prospective Randomized Controlled Study. Pharmacotherapy. 2015;35:470-6.

49. Nuraj P, Hyseni N. The Role of the Tamsulosin in the Medical Expulsion Therapy for Distal Ureteral Stones. Med Arch. 2017;71:137-40. Epub 2017/08/10. eng.

50. Pedro RN, Hinck B, Hendlin K, Feia K, Canales BK, Monga M. Alfuzosin stone expulsion therapy for distal ureteral calculi: a double-blind, placebo controlled study. J Urol. 2008;179:2244-7; discussion 7. Epub 2008/04/22. eng.

51. Pickard R, Starr K, MacLennan G, Lam T, Thomas R, Burr J, et al. Medical expulsive therapy in adults with ureteric colic: a multicentre, randomised, placebo-controlled trial. Lancet. 2015;386:341-9. Epub 2015/05/23. eng.

52. Sur RL, Shore N, L'Esperance J, Knudsen B, Gupta M, Olsen S, et al. Silodosin to facilitate passage of ureteral stones: a multi-institutional, randomized, double-blinded, placebo-controlled trial. European urology. 2015;67:959-64.

53. Wang CJ, Huang SW, Chang CH. Efficacy of an alpha1 blocker in expulsive therapy of lower ureteral stones. J Endourol. 2008;22:41-6.

54. Wang CJ, Tsai PC, Chang CH. Efficacy of Silodosin in Expulsive Therapy for Distal Ureteral Stones: A Randomized Double-blinded Controlled Trial. Urol J. 2016;13:2666-71. Epub 2016/06/29. eng.

55. Ye Z, Yang H, Li H, Zhang X, Deng Y, Zeng G, et al. A multicentre, prospective, randomized trial: comparative efficacy of tamsulosin and nifedipine in medical expulsive therapy for distal ureteric stones with renal colic. BJU Int. 2011;108:276-9. Epub 2010/11/19. eng.

56. Ye Z, Zeng G, Yang H, Tang K, Zhang X, Li H, et al. Efficacy and Safety of Tamsulosin in Medical Expulsive Therapy for Distal Ureteral Stones with Renal Colic: a Multicenter, Randomized, Double-blind, Placebo-controlled Trial. European urology. 2018;73:385-91.

57. Yuksel M, Yilmaz S, Tokgoz H, Yalcinkaya S, Bas S, Ipekci T, et al. Efficacy of silodosin in the treatment of distal ureteral stones 4 to 10 mm in diameter. International journal of clinical and experimental medicine. 2015;8:19086-92.

58. Porpiglia F, Destefanis P, Fiori C, Fontana D. Effectiveness of nifedipine and deflazacort in the management of distal ureter stones. Urology. 2000;56:579-82. Epub 2000/10/06. eng.

59. Porpiglia F, Ghignone G, Fiori C, Fontana D, Scarpa RM. Nifedipine versus tamsulosin for the management of lower ureteral stones. J Urol. 2004;172:568-71. Epub 2004/07/13. eng.

60. Balci M, Tuncel A, Aslan Y, Guzel O, Aydin O. Tamsulosin versus nifedipin in medical expulsive therapy for distal ureteral stone and predictive value of hounsfield unit in stone expulsion. Urology. 2014;84:S126.

61. Gandhi HR, Agrawal C. The efficacy of tamsulosin vs. nifedipine for the medical expulsive therapy of distal ureteric stones: A randomised clinical trial. Arab J Urol. 2013;11:405-10. Epub 2013/12/01. eng.

62. Zhang MY, Ding ST, Lu JJ, Lue YH, Zhang H, Xia QH. Comparison of tamsulosin with extracorporeal shock wave lithotripsy in treating distal ureteral stones. Chin Med J (Engl). 2009;122:798-801. Epub 2009/06/06. eng.

63. Mustafa A, Islam MS, Mamun AA, Khalid MS. Efficacy of tamsulosin in the medical management of juxtavesical ureteral stones: a randomized control trial. Bangladesh medical research council bulletin. 2016;42:78-83.

64. Sun X, He L, Ge W, Lv J. Efficacy of selective alpha1D-blocker naftopidil as medical expulsive therapy for distal ureteral stones. J Urol. 2009;181:1716-20. Epub 2009/02/24. eng.

65. Zhou SG, Lu JL, Hui JH. Comparing efficacy of alpha1D-receptor antagonist naftopidil and alpha1A/D-receptor antagonist tamsulosin in management of distal ureteral stones. World J Urol. 2011;29:767-71. Epub 2011/08/17. eng.

66. Kc HB, Shrestha A, Acharya GB, Basnet RB, Shah AK, Shrestha PM. Tamsulosin versus tadalafil as a medical expulsive therapy for distal ureteral stones: A prospective randomized study. Investig Clin Urol. 2016;57:351-6. Epub 2016/09/13. eng.

67. Puvvada S, Mylarappa P, Aggarwal K, Patil A, Joshi P, Desigowda R. Comparative efficacy of tadalafil versus tamsulosin as the medical expulsive therapy in lower ureteric stone: a prospective randomized trial. Central european journal of urology. 2016;69:178-82.

68. Shabana W, Teleb M, Dawod T, Abu Taha H, Abdulla A, Shahin AMS. A prospective randomized study to evaluate the outcome of alpha blockers and the combination with methylprednisolone in medical expulsive therapy for lower ureteral stones. European urology, supplements. 2015;14:e388.

69. Sun XH, He L, Ge WH, Lv JL. Efficacy of Selective alpha 1D-Blocker Naftopidil as Medical Expulsive Therapy for Distal Ureteral Stones. Journal of Urology. 2009;181:1716-20.

70. De Sio M, Autorino R, Di Lorenzo G, Damiano R, Giordano D, Cosentino L, et al. Medical expulsive treatment of distal-ureteral stones using tamsulosin: a single-center experience. J Endourol. 2006;20:12-6.

71. Shabana W, Teleb M, Dawod T, Abu Taha H, Abdulla A, Shahin A, et al. Outcome of α-blockers, with or without methylprednisolone combination, in medical expulsive therapy for lower ureteric stones: a prospective randomised study. Arab journal of urology. 2016;14:7-11.

72. Park HK, Choi EY, Jeong BC, Kim HH, Kim BK. Localizations and expressions of alpha-1A, alpha-1B and alpha-1D adrenoceptors in human ureter. Urological Research. 2007;35:325-9.

73. Itoh Y, Kojima Y, Yasui T, Tozawa K, Sasaki S, Kohri K. Examination of alpha 1 adrenoceptor subtypes in the human ureter. International Journal of Urology. 2007;14:749-53.

74. Sigala S, Dellabella M, Milanese G, Fornari S, Faccoli S, Palazzolo F, et al. Evidence for the presence of alpha1 adrenoceptor subtypes in the human ureter. Neurourol Urodyn. 2005;24:142-8.

75. Sridharan K, Sivaramakrishnan G. Efficacy and safety of alpha blockers in medical expulsive therapy for ureteral stones: a mixed treatment network meta-analysis and trial sequential analysis of randomized controlled clinical trials. 2018;11:291-307.

76. Laerum E, Ommundsen OE, Gronseth JE, Christiansen A, Fagertun HE. Oral diclofenac in the prophylactic treatment of recurrent renal colic. A double-blind comparison with placebo. Eur Urol. 1995;28:108-11.

77. Phillips E, Hinck B, Pedro R, Makhlouf A, Kriedberg C, Hendlin K, et al. Celecoxib in the management of acute renal colic: a randomized controlled clinical trial. Urology. 2009;74:994-9.

78. Liu H, Wang S, Zhu W, Lu J, Wang X, Yang W. Comparative efficacy of 22 drug interventions as medical expulsive therapy for ureteral stones: a systematic review and network meta-analysis. Urolithiasis. 2019.

79. Amer T, Osman B, Johnstone A, Mariappan M, Gupta A, Brattis N, et al. Medical expulsive therapy for ureteric stones: Analysing the evidence from systematic reviews and meta-analysis of powered double-blinded randomised controlled trials. Arab J Urol. 2017;15:83-93. Epub 2017/12/01. eng.

80. Marks LS, Gittelman MC, Hill LA, Volinn W, Hoel G. Rapid efficacy of the highly selective alpha1A-adrenoceptor antagonist silodosin in men with signs and symptoms of benign prostatic hyperplasia: pooled results of 2 phase 3 studies. J Urol. 2009;181:2634-40.

81. Hackenberger BK. Bayes or not Bayes, is this the question? Croat Med J. 2019;60:50-2.

Previous presentation in conferences : none

Conflict of interest: none to declare

Funding: none to declare

Acknowledgments: none

LEGENDS

Figure 1: PRISMA flow-chart depicting search strategy employed for this review.

Figure 2: Network plots for the two outcomes i.e. stone expulsion rate (SER) and stone expulsion time (SET)

Figure 3: Interval plots depicting mean risk ratio and standardized mean difference with respective 95% confidence intervals for stone expulsion rate and stone expulsion time respectively compared to control group.

Figure 4: Cluster rank plot for the two outcomes stone expulsion rate (A) and stone expulsion time (B)

Table 1: Characteristics of studies included in this review.

S.no	Author Year Country	Treatment (n)	Control (n)	Duration of treatment	Age (SD) (treatment vs. control)	Males/Females (treatment vs. control)	Stone size less than 10 mm	Mean st size (Treatm vs. cont
1	Al-Ansari 2010 Qatar	Tamsulosin 0.4mg	Placebo	4 weeks	37.1(9.4)/36.1(9.3)	23/8/35,15	Yes	5.8(2.4)

S.no	Author Year Country	Treatment (n)	Control (n)	Duration of treatment	Age (SD) (treatment vs. control)	Males/Females (treatment vs. control)	Stone size less than 10 mm	Mean st size (Treatm vs. cont
2	Aldemir 2010 Turkey	Group I- Tamsulosin 0.4mg Group II- Rowatinex 100mg thrice daily	Diclofenac 100 mg	10 days	42.4(16)/46.5(12.5)	22,8/17,13	Yes	6.7(1.4)
3	Alizadeh 2014 Iran	Tamsulosin 0.4 mg	No treatment	4 weeks	-	29,21/32,14	3-6 mm	-
4	Bajwa 2013 Pakistan	Tamsulosin 0.4 mg	Diclofenac 50 mg	4 weeks	32.4(8.3)/33.8(8.6)	18,12/19,11	Yes	6.9(1.4)
5	Cervenakov 2002 Slovakia	Tamsulosin 0.4 mg	Tramadol 50 mg Diazepan and Veral 50	-	-	32,19/33,18	Yes	-
6	ElGamal 2011 Egypt	Group II Tamsulosin 0.4mg	Group I Placebo control Group III Uralyt-U Group IV Uralyt-U plus tamsulosin	4 weeks	(Tamsulosin and placebo) 35.3(5.7)/36.2(8)	(Tamsulosin and placebo) 32,16/34,12	Yes	(Tamsu and placebo 7.9(1.9)
7	ElGalaly 2015 Egypt	Group I Tamsulosin 0.4 mg Group II Silodosin 8mg	-	4 weeks	Tamsulosin/Silodosin 35.5(11)/33.6(9.2)	Tamsulosin/Silodosin (32,19/35,17)	Yes	Tamsul (5.6(1.2
8	Vincendeau 2010 France	Tamsulosin 0.4 mg	Placebo	6 weeks	38.9(12)/39(11)	43,18/52,9	2-7 mm	2.9(1)/3
9	Yilmaz 2004 Turkey	Group II Tamsulosin 0.4mg Group III Terazosin 5mg Group IV Doxazosin 4mg	Group I No treatment	4 weeks	(Tamsulosin/control) 40.6(10),41.6(12)	(Tamsulosin/control) 22,20/19,9	Yes	(Tamsu 6(1.2)/6
10	Aggarwal 2009 India	I - Tamsulosin II – Alfuzosin	III - Placeo	4 weeks	I(31.4 yrs) II(38.7 yrs) III(35.3 yrs)	I(26/8) II(28/6) III(24/10)	Yes	I(6.17 m II(6.7m III(6.35 mm)

S.no	Author Year Country	Treatment (n)	Control (n)	Duration of treatment	Age (SD) (treatment vs. control)	Males/Females (treatment vs. control)	Stone size less than 10 mm	Mean st size (Treatm vs. cont
11	Ahmad 2015 Pakistan	I - Tamsulosin	II- Placebo	4 weeks	NA	4-10mm	<8mm	5.78mm
12	Cha 2012 Korea	I(Tamsulosin- 0.2mg OD) II(Tamsulosin - 0.2 mg BD) III(Alfuzosin) IV(Trospium)	-	4 weeks	I(45.07 yrs) II(45.5) III(42.33) IV(43.65	I(31/10) II(20/10) III(25/11) IV(18/16)	4-10mm	I(5.49m II(5.73r III(5.81 IV(5.59
13	Dell'atti 2015 Italy	I- Tamsulosin II- Silodosin	-	3 weeks	I(35 yrs) II(36 yrs)	I(39/27) II(44/23)	4-10mm	I(5.37r II(5.82r
14	Furyk 2015 Australia	I - Tamsulosin	II-Placebo	4 weeks	> 18 yrs	I(156/42) II(164/31	Yes	I(4mm) II(3.7m
15	Gomez 2011 Mexico	I- Tamsulosin	II-Placebo	4 weeks	I(38.5 yrs) II(38.2 yrs)	I(15/17) II(21/12)	5-10mm	I(5.3mm II(5.2m
16	Hermanns 2009 Switzerland	I- Tamsulosin	II-Placebo	3 weeks	I(36 yrs) II(41 yrs)	I(39/6) II(36/9)	7mm or less	I(4.1mm II(3.8m
17	Itoh 2013 Japan	II- Silodosin	I -Placebo	4 weeks	I(55.8 yrs) II(56.3 yrs)	all male	Yes	I(4.87m II(5.07r
18	Kumar 2015 India	I- Tamsulosin II- Silodosin III- Tadalafil	-	4 weeks	I(36.4 yrs) II(36.7 yrs) III(37.5 yrs)	I(62/28) II(64/26) III(67/23)	5-10mm	I(7.44m II(7.5m III(7.7m
19	Sameer 2014 India	I-Nifedipine II- Alfuzosin	III- Control	4 weeks	I(32.74 yrs) II(30.82 yrs) III(33.06 yrs)	I(19/16) II(26/9) III(23/12)	Yes	I(6.5mm II(6.28r III(6.37
20	Ahmad 2010 Saudi Arabia	I- Tamsulosin 0.4mg II- Alfuzosin 10mg	III- control- Diclofenac 75mg	30 days	I/II/III- 40.7(14.8)/41.1	I/II/III- (9,12)/(8,12)/(13,9)	Yes	I/II/III 4.97(2.2
21	Elsaid 2015 Egypt	Alfuzosin 5mg BD	control -Diclofenac + Hydration	4 weeks	Alfuzosin/Control- 32.8(9.5)/ 32.1(9.2)	Alfuzosin/control- 18,10/16,10	Yes	Alfuzos 6.3(2.1)
22	Nuraj 2017 Kosovo	I- Tamsulosin 0.4mg	Control- Diclofenac	4 weeks	Tamsulosin/Co	Tamsulosin/Co		Tamsulo 6.5(1.6)

S.no	Author Year Country	Treatment (n)	Control (n)	Duration of treatment	Age (SD) (treatment vs. control)	Males/Females (treatment vs. control)	Stone size less than 10 mm	Mean st size (Treatm vs. cont
23	Pedro 2008 USA	I- Alfuzosin	Placebo	4 weeks	Alfuzosin/Placebo 36.69(13.66)/ 42.03(12.85)	Alfuzosin/Placebo 28,6/27,8	Upto 8mm	Alfuzos 3.83(0.9
24	Pickard 2015 UK	I- Tamsulosin 0.4mg II- Nifedipine 30 mg	III- Placebo	4 weeks	I/II/III- 43.1(11.5)/42.3	I/II/III- 15,8/	Yes	I/II/III 4.6(1.6) 4.5(1.6)
25	Rahman 2017 India	I- Tamsulosin 0.4mg OD II- Silodosin 8 mg OD III- Silodosin 8mg + Tadalafil 5 mg		4 weeks	I/II/III- 38(10)/34(12)/ 35(10)	I/II/III- 24,16/22,18/25,15	5-10mm	I/II/III 7.5(1.20
26	Sur 2015 USA	I- Silodosin 8mg OD	II- Placebo	4 weeks	I/II- 47(13)/47(15)	I/II- 72,53/80,37	4-10mm	I/II- 5.4(1.4)
27	Wang 2008 Taiwan	I- Tamsulosin 0.4 mg OD II- Terazosin 2 mg OD	III- control	2 weeks	Tamsulosin/Terazosin/ 50.4(9.7)/ 51.4(8.6)/50.9(9.6)	I/II/III/Control 22,10/21,11/23,08	Yes	I/II/III 6.5(1.3)
28	Ye 2017 Wuhan, China	I- Tamsulosin 0.4mg	II- Placebo	4 weeks	I/II 40.1(11.6)/40.7	I/II- (12,8)	Yes	I/II- 5.8(1.9)
29	Sio 2006 Italy	I- Diclofenac 100mg/day + Aescin 80mg/day II- Diclofenac 100mg + Aescin 80mg + Tamsulosin 0.4 mg		2 weeks	I/II- 44.5(11.3)/46.3	I/II (10,9)/	Yes	I/II 6.4(1.3)
30	Wang 2015 Taiwan	I- Silodosin 8mg	II- control	2 weeks	51.4(8.6)/51.5	10,22/43,18	Yes	6.4(1.4)
31	Yuksel 2015 Turkey	Group II Silodosin 4 mg/day	Group I Placebo	3 weeks	Placebo/Silodosin 35.23(11.20) /35.31(11.55)	gp I /gp II 20,15/19,16	4-10mm	6.34(1.5 6.40(1.6

S.no	Author Year Country	Treatment (n)	Control (n)	Duration of treatment	Age (SD) (treatment vs. control)	Males/Females (treatment vs. control)	Stone size less than 10 mm	Mean st size (Treatm vs. cont
32	Porpiglia 2004 Italy	Group I- Nifedipine 30 mg + Deflazacort 30 mg x 10 days + Mysoprostol 200ug Group II- Tamsulosin 0.4 mg + Deflazacort 30 mg x 10 days + Mysoprostol 200ug	Group III- no expulsive therapy given	4 weeks	Group I/II/III- 45.6 (12)/ 50.5(17)/ 42.7 (16)	I/II/III- 19,11/ 18,10/ 16,12	<= 1 cm Yes	I/II/III 4.7 (1.4 5.42(1.5 5.35 (1.
33	DellaBella 2005 Italy	Group I- Phloroglucinol 80 mg 3 tabs OD Group II- Tamsulosin 0.4 mg OD Group III- Nifedipine SR 30 mg OD	Tab Cotrimoxazole 2 tabs OD x 8 days Tab. Deflazacort 30 mg OD x 10 days in each group	4 weeks	Group I/II/III 39.8 (12.7)/ 43.8 (13.9)/ 41.8(15.4)	I/II/III- 50/20, 54/16, 51/19	>4mm	I/II/III 6.2 (1.7 7.2 (2.4 6.2 (1.5
34	Ye 2011 China	Tamsulosin and nifedipine 3o mg	-	4 weeks	30.7(18-48)/34.5(22-50)	998,598/989,604		
35	Balci 2014 Turkey	Tamsulosin and nifedipine 3o mg		4 weeks	39.5(12)/36.4(11.7)	18,7/17,8		7(1.5)/6
36	Gandhi 2013 Nepal	Tamsulosin and nifedipine 3o mg	-	4 weeks	34(12.8)/30.4(11.2)	38,26/36,28		8.6(2.3)
37	Shokeir 2016 Egypt	II-Sildenafil	I-Placebo	4 Weeks	45.3 yrs 45.8yrs	NA	Yes	NA
38	Zhang 2009 China	Tamsulosin and nifedipine 3o mg	-	4 weeks	34.6(11.4)/36.3(13.2)	39,29/68,29	Yes	6.9(1.6)

S.no	Author Year Country	Treatment (n)	Control (n)	Duration of treatment	Age (SD) (treatment vs. control)	Males/Females (treatment vs. control)	Stone size less than 10 mm	Mean st size (Treatm vs. cont
39	Islam Bangladesh	Tamsulosin and nifedipine 2o mg	-	4 weeks	46.6/47.4	20,12/21,10		5.9(3-10)/6(3 10)
40	Lv 2014 China	Group I - Naftopidil 50mg/day Group II- Naftopidil 50 mg/day + Celecoxib 200mg BD	Group III -Celecoxib 200 mg BD	2 weeks	Group I/II/III 31.40 ± 3.94/ 33.20 ± 5.28/ 33.75 ± 5.24	Group I/II/III 20/15, 21/14, 18/15	4-9mm	I/II/III ± 1.30 7.1 ± 1 7.3 ± 1
41	Sun 2008 China	Group II- Naftopidil 50 mg OD	Group I - control No MET given	2 weeks	Group I/II- Control/ Naftopidil 37.8(10.2)/ 38.2 (12.6)	Control/Naftopidil- 24/6 , 26/4		Control Naftopi 5.7 (1.2 5.5 (1.2
42	Zhou 2011 China	Group I- Naftopidil 10 mg OD Group II- Tamsulosin 0.4 mg OD	Group III- control no MET	2 weeks	group I/II/III- 33.73 ± 8.84/ 34.42 ± 8.64/ 34.79 ± 9.63	Group I/II/III- 25/18. 27/18, 27/16	Yes 4-9 mm	Group I/II/III 6.67 ± 6.54 ± 6.61 ±
43	Kumar 2013 India	I Naftopidil II tamsulosin Pred-nisolone given to both groups	III control	4 weeks	33.2/33.2/33.5-		6.9/7.1/6.6	5-10 mr
44	Kumar 2014 India	I- Tamsulosin II- Tamsulosin +Tadalafil	Prednisolone given to both groups	6 Weeks	I(32.45 yrs) II(35.23 yrs)	I(19/12) II(25/6)	Yes	I(7.05m II(6.67r
45	KC 2016 Nepal	I- Tamsulosin II- Tadalafil	NA	2 Weeks	I(31.37 yrs) II(32.05 yrs)	I(27/14) II(24/20)	Yes	I(7.09m II(7.13r
46	Puvvada 2016 India	I-Tadalafil II- Tamsulosin	NA	4 Weeks	I(36.34 yrs) II(37.53 yrs)	I(65/35) II(67/33)	Yes	I(7.10m II(7.22r

S.no	Author Year Country	Treatment (n)	Control (n)	Duration of treatment	Age (SD) (treatment vs. control)	Males/Females (treatment vs. control)	Stone size less than 10 mm	Mean st size (Treatm vs. cont
47	Jayant 2014 India	I- Tamsulosin II- Tamsulosin+Tadalafil	NA	4 weeks	I(36.45 yrs) II(37.23 yrs)	I(65/57) II(67/55)	Yes	I(6.72m II(7.05r
48	Porpiglia 2000 Italy	Group A: Deflazacort 30mg for 10 days and Nifedipine 30 mg	Group b: no treatment	4 weeks	-	26,22/24,24	5.8(18)/5.5(1.4)	< 10mr
49	Shabana 2016 Egypt	Group A: Tamsulosin Group B: Tamsulosin plus methyl-pred-nisolone Group C: Alfuzosin Group D: Alfuzosin plus methylprednisolone	-	2 weeks	53/51/49/49	30,23/29,24/31,22/27,22	7,8/8,7/6,9/8	Yes
50	Borghi 1994 Italy	Nifedipine plus methylprednisolone	Placebo	45 days	-	-	6.7/6.8	Yes

Table 2: League table for the primary outcome i.e stone expulsion rate.

AL	0.71(0.506, 1.006)	**1.330 (1.129, 1.566)**	0.829 (0.618, 1.113)	0.546 (0.363, 0.821)	1.217 (1.0
1.401 (0.994, 1.974)	AL-S	**1.862 (1.328, 2.612)**	1.162 (0.766, 1.763)	0.764 (0.476, 1.226)	1.705 (1.1
0.752 (0.639, 0.886)	0.537 (0.383, 0.753)	**C**	0.624 (0.486, 0.801)	0.410 (0.278, 0.605)	0.915 (0.7
1.206 (0.899, 1.618)	0.861 (0.567, 1.306)	**1.603 (1.248, 2.060)**	NAF	0.658 (0.415, 1.042)	1.468 (1.1
1.833 (1.219, 2.757)	1.309 (0.816, 2.100)	**2.437 (1.654, 3.592)**	1.520 (0.960, 2.408)	NAF-S	2.231 (1.4
0.822 (0.677, 0.997)	0.587 (0.410, 0.838)	**1.092 (0.944, 1.265)**	0.681 (0.514, 0.904)	0.448 (0.297, 0.675)	NIF
1.213 (0.919, 1.602)	0.866 (0.596, 1.258)	**1.613 (1.265, 2.057)**	1.006 (0.711, 1.424)	0.662 (0.446, 0.982)	1.477 (1.1
1.253 (0.746, 2.106)	0.894 (0.492, 1.626)	**1.666 (1.018, 2.727)**	1.039 (0.598, 1.806)	0.684 (0.365, 1.279)	1.525 (0.9
1.203 (0.978, 1.479)	0.859 (0.599, 1.232)	**1.600 (1.387, 1.844)**	0.998 (0.752, 1.324)	0.656 (0.435, 0.989)	1.464 (1.2
1.151 (0.894, 1.483)	0.822 (0.557, 1.213)	**1.531 (1.240, 1.889)**	0.955 (0.693, 1.315)	0.628 (0.405, 0.973)	1.401 (1.1
1.455 (1.018, 2.079)	1.038 (0.653, 1.651)	**1.934 (1.396, 2.680)**	1.206 (0.803, 1.812)	0.794 (0.479, 1.314)	1.770 (1.2
1.265 (0.879, 1.820)	0.903 (0.565, 1.443)	**1.682 (1.201, 2.355)**	1.049 (0.694, 1.586)	0.690 (0.414, 1.149)	1.539 (1.0
1.602 (0.999, 2.568)	1.144 (0.681, 1.921)	**2.130 (1.347, 3.368)**	1.329 (0.790, 2.236)	0.874 (0.518, 1.473)	1.950 (1.2
0.992 (0.846, 1.163)	0.708 (0.506, 0.991)	**1.319 (1.217, 1.429)**	0.823 (0.639, 1.060)	0.541 (0.366, 0.800)	1.207 (1.0
1.417 (1.084, 1.852)	1.012 (0.718, 1.426)	**1.884 (1.479, 2.401)**	1.175 (0.832, 1.661)	0.773 (0.545, 1.096)	1.725 (1.3