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Which combination of medical expulsive therapy is more effective for treatment of distal ureteral stone in adults? A systematic review and network meta-analysis

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Abstract

Background Medical Expulsive Therapy (MET) has been recommended as an established modality for the treatment of distal ureteral stones due to its clearance rate, pain control, and patient satisfaction while having minimal morbidity in comparison to other urologic interventions. In some studies, a combination of medications has been used, which we assessed in this network meta-analysis (NMA).

Methods We conducted systematic searches in PubMed, Scopus, and Web of Science to identify relevant trials published between 2001 and 2024. We excluded articles that looked at MET for upper ureteral stone passage or after shock wave lithotripsy (SWL). NMA was performed to compare the effect of combination MET on stone expulsion rate (SER), stone expulsion time (SET), and need for analgesia.

Results We included 19 studies with 2414 participants. NMA results revealed that the combination MET of α-blockers with PDE-5 inhibitors (OR = 2.7, CI = 1.80,4.05), corticosteroids (OR = 2.7, CI = 1.81,4.13), and phytotherapy (OR: 3.10, CI = 1.62,5.92) were more effective than α-blockers alone in SER. The combination MET of α-blockers with PDE-5 inhibitors (MD: -3.8, CI=-7.0, -0.5) showed significantly lower SET compared to α-blockers alone. Finally, combination MET of α-blockers with PDE-5 inhibitors (MD:1.0, CI = 0.4,1.7) and nifedipine with corticosteroids (MD:1.2, CI = 0.4,1.9) showed a significant decrease in analgesia use.

Conclusions The combination MET of α-blockers with PDE-5 inhibitors, corticosteroids, and phytotherapy increases the rate of stone clearance 2.7 to 3.1 times more than α-blockers alone. The other benefits of combination MET were lower expulsion time and less analgesia use that needs further studies.

Keywords Alpha-blockers, Drug combination, Kidney stone, Medical expulsive therapy, Ureterolithiasis

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Background

Urolithiasis is a prevalent disease in all around of the world [1]. The estimated prevalence rate of kidney stone is 7 to 13% in North America, between 5 and 9% in Europe, and 1–5% in Asia [1, 2]. A total of 22% of all urinary tract stones are found in the ureter, of which 68% are seen in the distal part of ureter [3]. Current therapeutic options for distal ureteral stone include extracorporeal SWL, ureteroscopy, laparoscopic/robotic or open surgical removal, MET, and watchful waiting for spontaneous stone passage [4, 5].

Conservative medical treatment or watchful waiting approach is usually indicated to facilitate the clearance of 6–10 mm uncomplicated distal ureteral stones. However, the simple watchful waiting approach can result in complications, such as urinary tract infection, hydronephrosis, or impaired renal function [6]. It is important to note that conservative approaches such as MET or watchful waiting is recommended for four to six weeks because of irreversible renal parenchymal damage in the context of obstructing ureteral stones [7]. Therefore, the watchful waiting approach is extended by using pharmacologic treatment in order to facilitate stone clearance in the last two decades [8]. The medications generally used as MET are either agents which decrease the peristaltic contraction of the ureteral smooth muscle (α1-adrenoreceptor antagonists; α-blockers, calcium channel blockers; nifedipine or phosphodiesterase-5 inhibitors; PDE5-Is) or antiedemic agents such as corticosteroids for reducing the inflammation of ureteral mucosa [9]. It is worth mentioning that this is an off-label recommendation. α-blockers cause ureteral smooth muscle relaxation with maintenance of normal antegrade peristaltic activity that facilitates the passage of stones [3, 10], and PDE5-Is act on nitric oxide pathway, which influence smooth muscle tone [11, 12]. In addition to these two known drug groups, some phytotherapy medications such as rowatinex or phloroglucinol have also been used to help ureteral stone expulsion, whose mechanism of action is not well understood.

Some previous studies suggest that the combination of medications mentioned above (as combination MET) is a reasonable way to increase their effects on SER, lower SET, and mean analgesia use (MAU) [13]. To assess this hypothesis, we conducted a network meta-analysis (NMA) on studies that looked at the use of combination MET in adults with distal ureteral stones and compared their results with each other.

Methods

Search strategy and data extraction

A comprehensive literature search was conducted on PubMed, Scopus, and Web of Science for studies published from 2001 to April 2024, which included combination MET on distal ureteral stone in adults, with no language restrictions. We used the following search terms: "medical expuls*" AND (nephrolithiasis OR stone) AND ureter. We also searched the reference lists of retrieved articles to find relevant studies. We clarified that only comparative studies with a minimum number of 10 cases were included to ensure a sufficient sample size for meaningful analysis. We excluded irrelevant and duplicate studies, meta-analysis, review articles, case reports, letters, or recommendations. We also excluded studies that used combination MET for upper ureteral stone clearance or after shock wave lithotripsy. Two reviewers (SN, SSh) independently screened the titles and abstracts of the identified studies and assessed the full texts of the eligible trials. Any disagreement was resolved by consulting a third reviewer (PZ). We extracted data on study characteristics, interventions, outcomes, and risk of bias.

As the prescribed dosage for medications in the α-blockers, PDE5-Is and corticosteroids were based on their standard dosage, the different medications of the above-mentioned groups were considered pharmacologically equivalent and categorized in their respective pharmacologic groups. Accordingly, we included tamsulosin, alfuzosin, silodosin, and naftopidil in the α-blockers group; tadalafil and vardenafil in the PDE5-Is group: and prednisolone, methylprednisolone, and deflazacort in the corticosteroids group. Since α-blockers are commonly used as MET in monotherapy [6], the included studies were classified into the following subgroups: α-blockers + PDE5-Is, α-blockers and corticosteroids, α-blockers and phytotherapy, and combination therapy without α-blockers. Other studies not included in the above classifications, were placed in two groups of miscellaneous combination MET or miscellaneous monotherapy.

The ethics committee of the Urology and Nephrology Research Center (Shahid Beheshti University of Medical Sciences, Tehran, Iran) approved the study protocol (IR.SBMU.UNRC.REC.1402.004).

Outcome measures

The primary outcome of the current study was SER, which was defined as the percentage of patients who passed the stone at the time of follow-up visit. The secondary outcomes were assessing SET and MAU. SET was defined as the number of days from the start of treatment to the self-reported passage of the stone or confirmation by follow-up imaging, and MAU was defined as the average number of consumed pain killers during the treatment period.

Risk of bias and data extraction

The methodological quality of included studies was assessed using the Cochrane Assessment of Risk of Bias tool in five domains: selection of the reported outcome, measurement of the outcome, missing outcome data, deviations from intended interventions, and randomization process. We rated the risk of bias in each domain as low, high, or unclear. Two independent researchers (MT, NB) performed the assessment, any disagreements were resolved by discussion. Results of risk of bias assessment showed that most studies have some concern or low risk of bias in all categories (Figure 1).

Statistical methods

Pairwise meta-analyses with direct evidence were conducted for all comparisons using a random-effects model. To assess the heterogeneity among the studies in.

pairwise comparison, the I^2 statistics was calculated. Network meta-analysis was performed to evaluate the efficacy of multiple interventions, using a frequentist model [14]. Risk ratios (for dichotomous outcomes) or standardized mean differences (for continuous outcomes) were reported with their 95% confidence intervals. The analyses were done using 'netmeta' package in R 4.1.2.

Results

Studies included and their characteristics

We searched three databases and other sources, and identified 385 articles relevant to the research question. We excluded 336 records which did not meet our inclusion criteria and retrieved 32 studies for further consideration. Finally, we excluded 13 more records because of methodological or reporting issues, and included 19 studies in our final analysis. Figure 2 presents the PRISMA flow chart describing the inclusion process. Table 1 shows the aggregated characteristics of the included studies. The maximum ureteral stone size was ≤ 10 mm in 14 and ≤ 15 in three studies. The follow-up time were ≤ 14 days in three studies, ≤ 30 days in 14 studies, and up to a maximum of 45 days in three studies. The mean treatment days for some monotherapy and combination MET groups were as follows: α-blockers alone; 24.73 days, miscellaneous monotherapy: 20.4 days, α-blockers + PDE5-Is:26.25 days, α-blockers + corticosteroids: 26 days, α-blockers + phytotherapy: 32.5 days, nifedipine + corticosteroids: 30.25 days, and miscellaneous combination MET groups: 28.6 days.

Treatment outcomes

Table 2 represents the results of pair-wise meta-analyses (in upper triangle of the Table) and a network meta-analysis (in lower triangle of the Table), which shows the odds ratio (OR) and 95% confidence interval (CI) of SER for each pair of medical treatment groups. The NMA results in the Table presents the row-defining treatment versus the column-defining treatment. An OR greater than 1 favors the row-defining treatment, and an OR less than 1 favors the column-defining treatment. For example, the OR (95% CI) comparing α-blockers + corticosteroids versus α-blockers alone are 2.73 (1.81, 4.13) based on NMA. This means that α-blockers + corticosteroids are more effective than α-blockers alone in SER outcome. In addition, these results suggest that combination MET of

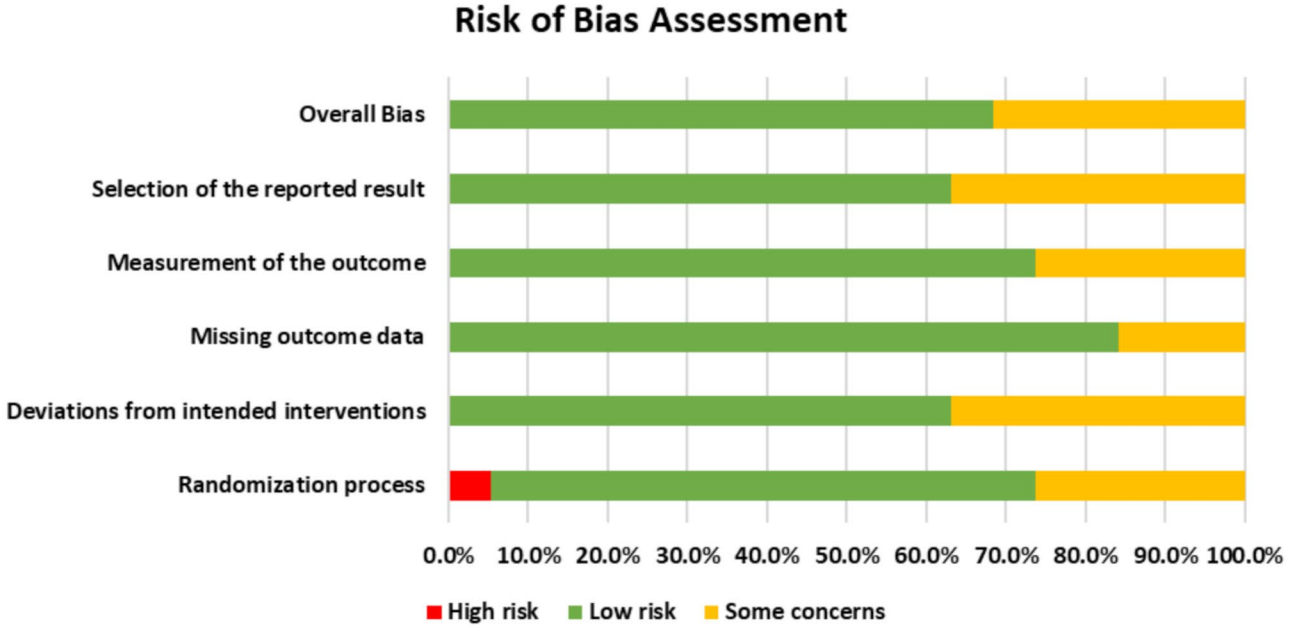

Fig. 1 Risk of bias in included studies

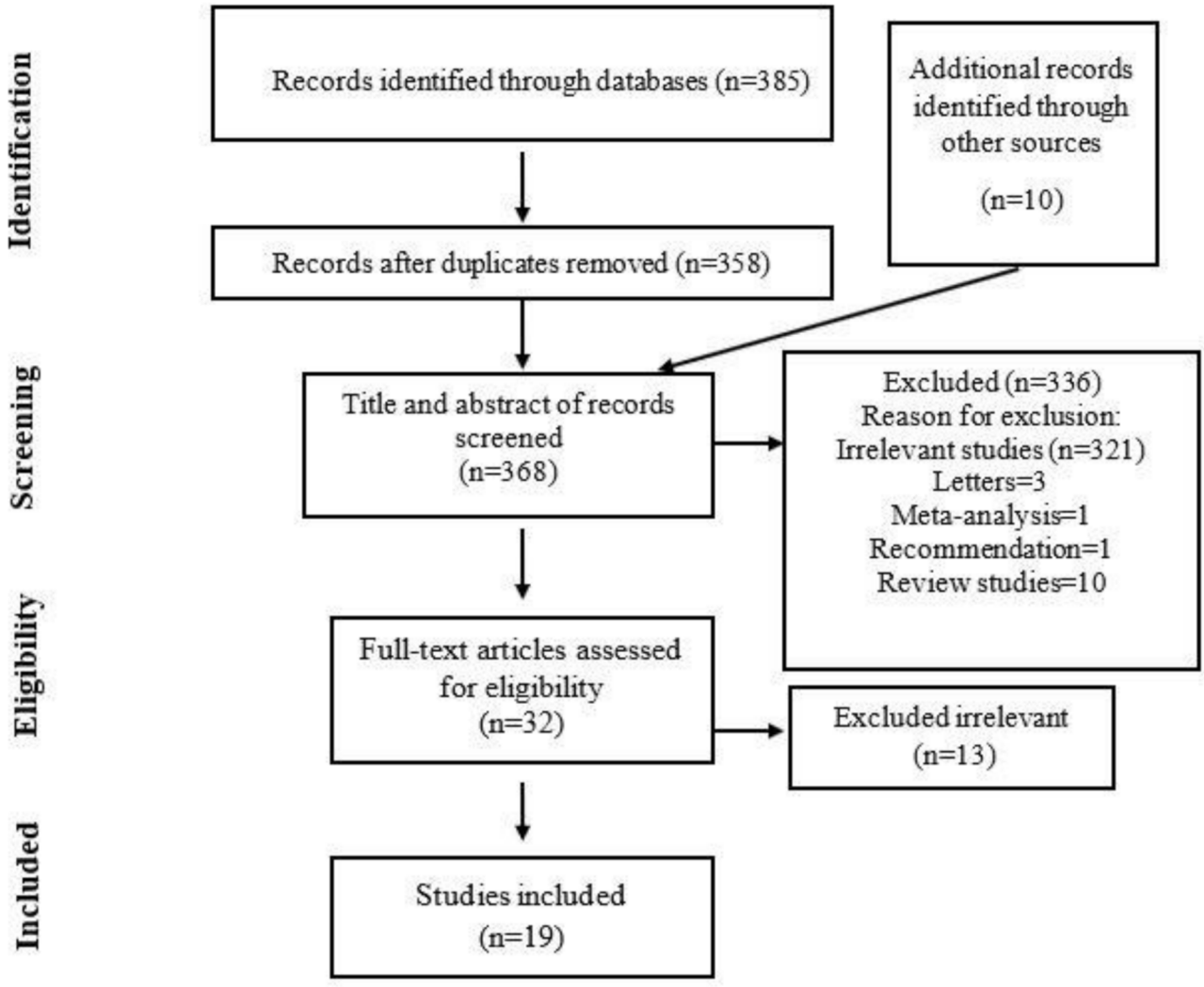

Fig. 2 Flow chart for inclusion of studies

α-blockers + PDE5-Is and α-blockers + phytotherapy are more effective than a-blockers alone. However, there is no significant difference between α-blockers + phytotherapy, α-blockers + PDE5-Is and or α-blockers + corticosteroids in SER. Finally, α-blockers + corticosteroids and α-blockers + PDE5-Is have similar effectiveness. In addition, nifedipine + corticosteroids seem more effective than corticosteroids alone or other monotherapy groups. However, nifedipine + corticosteroids exhibited lower efficacy when compared to any combination MET of α-blockers with PDE5-Is, corticosteroids or phytotherapy groups. Similarly, NMA results revealed that corticosteroids alone had lower efficacy to α-blockers alone regarding SER.

The results suggest that combination of α-blockers with PDE5-Is, corticosteroids or phytotherapy were the most effective treatment groups. The second most effective treatment group was nifedipine + corticosteroids. The least effective treatments groups were miscellaneous combination MET or miscellaneous monotherapy, corticosteroids or PDE-5 inhibitors alone and watchful waiting. These treatments had an OR less than 1 for most comparisons, indicating that they were inferior to the other treatment groups.

The NMA results for SET and MAU were derived from 15 to 8 studies, respectively. Table 3 shows the comparisons of the study intervention groups for the SET (the left lower triangle) and MAU (the right upper triangle) using mean difference (MD) and 95% CI. The row-defining treatment is compared to the column-defining treatment. The results indicate that α-blockers alone or combined with PDE5-Is, corticosteroids or phytotherapy reduced SET and MAU compared to the other groups. Expulsion time was significantly lower in α-blockers + PDE5-Is group compared to α-blockers alone or miscellaneous monotherapy groups. For MAU, there was a

Table 1 Characteristics of included studies in this network meta-analysis

	First author	Stone size (mm)	Total participants (Male/Female)	Age Mean (SD)/Median (IQR)	Intervention groups/ Number	F/U (days)	SER (%)	SET (days) Mean (SD)/ Median (IQR)	MAU (Number)
1.	Gnyawali D. (2020) [10]	5–10	161 (108/53)	32.85 (10.36) 33.75 (10.01)	-Tamsulosin (0.4 mg/d.)/ 80 -Tamsulosin (0.4 mg/d.) + Tadalafil (10 mg/d.)/ 81	21	62.5% 79.0%	16.24 (5.32) 11.62 (6.09)	526 (86) † 403 (131)
2.	Jayant K. (2014) [3]	5–10	244 (132/112)	36.45 (10.36) 37.23 (12.54)	-Tamsulosin (0.4 mg/d.)/ 122 -Tamsulosin (0.4 mg/d.) + Tadalafil (10 mg/d.)/ 122	28	65.5% 83.6%	16.7 (4.8) 14.9 (4.4)	2.90 (0.90) 1.87 (0.8)
3.	Rahman M.J. (2017) [12]	5–10	120 (71/49)	38 (10) 34 (12) 35 (10)	-Tamsulosin (0.4 mg/d.)/ 40 -Silodosin (8 mg/d.)/ 40 -Silodosin (8 mg/d.) + Tadalafil (5 mg/d.)/ 40	28	57.5% 77.5% 90%	21 (4.6) 15 (3.3) 12 (2.2)	NA
4.	Samir M. (2020) [15]	6–10	90 (all male)	38.67 (6.82) 37.63 (8.77) 36.90 (9.23)	-Silodosin (8 mg/d.)/ 30 -Vardenafil (5 mg/d.)/ 30 -Silodosin (8 mg/d.) + Vardenafil (5 mg/d.)/ 30	28	76.7% 60.0% 90.0%	12.5 (1.66) 14.67 (1.24) 11.23 (3.14)	613.44 (483.62) † 716.97 (685.3) 313.6 (285.5)
5.	Gandhi H.R. (2013) [24]	5–15	122 (71/51)	34.0 (12.83) 30.4 (11.36)	-Tamsulosin (0.4 mg/d.) + Prednisolone (30 mg/d./10 days)/ 64 -Nifedipine (30 mg/d.) + Prednisolone (30 mg/d.)/ 64	28	79.7% 55.2%	23 9	1.19 (0.59) 0.42 (0.14)
6.	Kumar S. (2014) [34]	5–10	62 (44/18)	32.45 (9.36) 35.23 (13.54)	-Tamsulosin (0.4 mg/d.) + Prednisolone (5 mg/d./7 days)/ 31 -Tamsulosin (0.4 mg/d.) + Tadalafil (10 mg/d.) + Prednisolone (5 mg/d.)/ 31	42	74.2% 83.9%	18.9 (8.7) 15.15 (5.5)	2.90 (0.90) 1.87 (1.38)
7.	Kumar S. (2013) [35]	5–10	120 (83/37)	33.2 (10.5) 33.2 (8.5) 33.5 (10.3)	-Tamsulosin (0.4 mg/d.) + Prednisolone (5 mg/d./7 days)/ 40 -Naftopidil (75 mg/d.) + Prednisolone (5 mg/d.)/ 40 -Watchful waiting/ 40	28	70.0% 87.5% 32.5%	8.7 (1.5) 9.1 (2.1) 14.0 (2.2)	2.4 (1.2) 2.1 (0.9) 4.1 (0.7)
8.	Hwang EC (2012) [25]	< 10	113 (63/50)	52.3 (9.79) 53.8 (9.04)	-Alfuzosin (10 mg/d.) + Methylprednisolone (8 mg/d./28 days) + Ketorolac (10 mg/BD)/ 47 -Ketorolac (10 mg/BD)/ 66	28	82.9% 62.1%	4.4 (3.23) 7.3 (4.87)	0.8 (0.36) 2.1 (1.17)
9.	Shabana W. (2016) [23]	≤ 10	212 (117/95)	53 (1.5) 51 (3.6) 49 (2.7) 48 (4.1)	-Tamsulosin (0.4 mg/d.)/ 53 -Tamsulosin (0.4 mg/d.) + Methylprednisolone (8 mg/d./14 days) / 53 -Alfuzosin (10 mg/d.) / 53 -Alfuzosin (10 mg/d.) + Methylprednisolone (8 mg/d./14 days) / 53	14	54.7% 71.9% 52.8% 73.6%	13 10 12 9	2.3 (1.1) 1.9 (0.9) 2.1 (1.3) 1.8 (1)
10.	Kucukpolat S. (2019) [22]	4–10	134 (87/47)	39.2 (18–60) 35.6 (19–59) 40.4 (23–59) 45.5 (29–64)	-Tamsulosin (0.4 mg/d.)/ 37 -Deflazacort (30 mg/d./28 days)/ 26 -Tamsulosin (0.4 mg/d.) + Deflazacort (30 mg/d./28 days)/ 37 -Watchful waiting/ 34	28	64.8% 69.2% 75.7% 26.4%	NA	NA
11.	Porpoglia F. (2006) [9]	5–8	114 (72/42)	47.8 (1.3) 45.3 (2.2) 48.2 (0.6) 45.2 (0.88)	-Tamsulosin (0.4 mg/d.)/ 33 -Deflazacort (30 mg/d./10 days)/ 24 -Tamsulosin (0.4 mg/d.) + Deflazacort (30 mg/d./10 days)/ 33 -Watchful waiting/ 24	10	60% 37.5% 84.8% 33.3%	NA	42.5 (0.4) 50 (0.3) 27.3 (0.5) 81 (0.33)
12.	Dellabella M. (2005) [17]	≥ 4	60 (43/17)	43.2 (13.3) 45.8 (14.8)	-Tamsulosin (0.4 mg/d.)/ 30 -Tamsulosin (0.4 mg/d.) + Deflazacort (30 mg/d./10 days)/ 30	28	90% 96.7%	5 (2.96) 3 (2.96)	0.41 (0.75) 0.24 (0.51)
13.	Dellabella M. (2005) [28]	4–18	210 (155/55)	43.8 (13.9) 41.8 (15.4) 39.8 (12.7)	-Tamsulosin (0.4 mg/d.) + Deflazacort (30 mg/d./10 days)/ 70 -Nifedipine (30 mg/d.) + Deflazacort (30 mg/d./10 days)/ 70 -Phloroglucinol (80 mg/TDS) + Deflazacort (30 mg/d./10 days)/ 70	28	97.1% 77.1% 64.3%	3 (2.96) 5 (1.48) 5 (2.96)	0 (0–0) 1(0–1) 2 (1–5)

Table 1 (continued)

	First author	Stone size (mm)	Total participants (Male/Female)	Age Mean (SD)/Median (IQR)	Intervention groups/ Number	F/U (days)	SER (%)	SET (days) Mean (SD)/ Median (IQR)	MAU (Number)
14.	Jang WK. (2008) [36]	≤ 7	180 (106/74)	47.9 (17–72) 49.3 (22–70) 48.3 (23–64)	-Tamsulosin (0.4 mg/d.) + Deflazacort (24 mg/d./14 days) + Furosemide (40 mg/d.)/ 72 -Tamsulosin (0.4 mg/d.) + Furosemide (40 mg/d.)/ 66 -Furosemide (40 mg/d.)/ 42	14	91.7% 80.3% 64.3%	NA	NA
15.	Faragi G. (2008) [37]	≤ 5	67 (56/12)	44 (44) 43 (42) 45 (44)	-Alfuzosin (10 mg/d.)/ 22 -Rowatinex (12 capsules/d.)/ 19 -Alfuzosin (10 mg/d.) + Rowatinex (12 capsules/d.)/ 26	30	77% 74% 96%	7.4 (5) 13.7 (11) 5.2 (3)	NA
16.	Shafique MN. (2018) [13]	3–8	64 (52/12)	41.12 (4.8) 43.84 (6.7)	-Tamsulosin (0.4 mg/d.)/ 32 -Tamsulosin (0.4 mg/d.) + Phloroglucinol (40 mg/BD)/ 32	42	81.2% 100%	17.69 (2.8) 10.34 (3.5)	29.69 * 12.50
17.	Palmisano F. (2018) [29]	4–10	228 (168/60)	47.7 (15.2) 47.6 (15.7)	-Tamsulosin (0.4 mg/d.)/ 114 -Tamsulosin (0.4 mg/d.) + Bromelain (500 mg/d.)/ 114	30	75.4% 87.7%	11.57 (6.72) 11.68 (6.96)	NA
18.	Borghi L. (1994) [16]	< 15	76 (51/25)	45 (14) 43 (14)	-Nifedipine (40 mg/d.) + Methylprednisolone (16 mg/d./45 days)/ 39 -Placebo + Methylprednisolone (16 mg/d./45 days)/ 37	45	87.2% 64.9%	11.2 (7.5) 16.4 (11)	NA
19.	Saita A. (2004) [38]	≤ 15	37 (NA)	NA	-Nifedipine (30 mg/d.) + Prednisolone (25 mg/d./10 days)/ 19 -Prednisolone (25 mg/d./10 days)/ 18	20	81% 68%	6 (5.92) 10 (7.4)	NA

F/U: Follow up, SER: stone expulsion rate, SET: stone expulsion time, MAU: Mean Analgesia use, BD: "bis in die" that means twice daily, TDS: Three times a day

† Milligram of analgesic drug were reported in the current study

Table 2 Summary of the results for the primary outcome (stone expulsion rate) of the network meta-analysis (the left lower triangle) and pairwise meta-analysis (the right upper triangle). Bold numbers indicate statistically significant results ($p < 0.05$)

Pair-wise meta-analysis									
α-blocs	**0.41(0.26,0.64)**	**0.37(0.24,0.55)**	**0.31(0.16,0.60)**	-	1.27(0.60,2.69)	1.21(0.29,5.06)	-	2.19(0.71,6.69)	1.21(0.58,2.49)
2.73(1.81,4.13)	α-blocs + Steroids	-	-	**3.50(1.63,7.47)**	**3.25(1.47,7.16)**	**2.97(1.19,7.37)**	**3.91(1.98,7.70)**	-	**4.35(2.47,7.65)**
2.70(1.80,4.05)	0.98(0.55,1.76)	α-blocs + PD5-Is	-	-	-	-	-	**6.0(1.48,24.29)**	-
3.10(1.62,5.92)	1.13(0.53,2.42)	1.14(0.53,2.46)	α-blocs + Phyto	-	-	8.92(0.94,84.24)	-	-	-
1.38(0.68,2.77)	**0.50(0.27,0.92)**	0.51(0.22,1.14)	0.44(0.17,1.13)	Misc Com*	-	**3.47(1.57,7.70)**	0.53(0.25,1.11)	-	-
0.66(0.35,1.24)	**0.24(0.13,0.44)**	**0.24(0.11,0.51)**	**0.21(0.08,0.52)**	0.48(0.22,1.04)	Steroids	-	**0.34(0.14,0.85)**	-	0.97(0.43,2.20)
0.59(0.29,1.18)	**0.21(0.11,0.40)**	**0.21(0.09,0.48)**	**0.18(0.07,0.47)**	**0.42(0.22,0.80)**	0.88(0.39,1.99)	Misc Mono**	-	-	-
1.58(0.83,3.0)	**0.57(0.33,0.99)**	0.58(0.27,1.24)	0.50(0.20,1.25)	1.14(0.62,2.09)	**2.37(1.24,4.52)**	**2.68(1.29,5.57)**	Nif + Steroids	-	-
0.45(0.16,1.25)	**0.16(0.05,0.49)**	**0.16(0.06,0.47)**	**0.14(0.04,0.48)**	0.32(0.09,1.12)	0.68(0.20,2.23)	0.77(0.22,2.63)	0.28(0.08,0.95)	PD5-Is	-
0.63(0.35,1.12)	**0.23(0.13,0.39)**	**0.23(0.11,0.47)**	**0.20(0.08,0.48)**	**0.45,0.20,0.99)**	0.94(0.47,1.88)	1.07(0.48,2.37)	0.39(0.19,0.82)	1.39(0.43,4.47)	Wait
Network meta-analysis									

Data are the odds ratio with 95% CI (OR). On the left lower triangle, the row-defining drug intervention is compared with the column-defining drug intervention, and an OR > 1 favors the row-defining drug intervention. On the right upper triangle, the row-defining drug intervention is compared with the column-defining drug intervention, and a OR > 1 favors the row-defining drug intervention. α-blocs. α-blockers, PDE5-Is. PDE-5 inhibitors, Steroids. Corticosteroids, Wait. Watchful waiting, α-blocs + PDE5-Is. α-blockers, α-blocs + Steroids. α-blockers + Corticosteroids, α-blocs + Phyto. α-blockers + Phytotherapy, Nif + Steroids. Nifedipine + Corticosteroids, Misc Com. Miscellaneous Combination therapy, Misc Mono. Miscellaneous Monotherapy

*Miscellaneous Combination groups included; Tamsulosin (0.4 mg/d.) + Tadalafil (10 mg/d.) + Prednisolone, Phloroglucinol (80 mg/TDS) + Deflazacort (30 mg/d.), Phloroglucinol (80 mg/TDS) + Deflazacort (30 mg/d.), Tamsulosin (0.4 mg/d.) + Deflazacort (24 mg/d.) + Furosemide (40 mg/d.), and Tamsulosin (0.4 mg/d.) + Furosemide (40 mg/d.). **Miscellaneous monotherapy groups included; Rowatinex, Ketorolac, and Furosemide

significant reduction in α-blockers + PDE5-Is compared to α-blockers + corticosteroids and α-blockers alone. Moreover, a significant reduction in MAU was observed for α-blockers alone, α-blockers + PDE5-Is and miscellaneous combination MET, when compared with miscellaneous monotherapy groups. In addition, α-blockers alone, α-blockers + corticosteroids and miscellaneous monotherapy groups increased the MAU significantly when compared with nifedipine + corticosteroids. There was no difference between other treatments in either outcome. Network map for the stone expulsion rate is presented in Figure 3.

Drug Side Effects. Common α-blockers side effects such as headache, dizziness, postural hypotension, backache and retrograde ejaculation, were reported in some participants who were treated symptomatically without the need to discontinue the medication. 5-PDIs showed some degree of penile intumescence without any report of priapism [3, 10, 11, 15]. Regarding corticosteroids, dyspepsia was reported in some patients, but all of them complete the trial. In one study five participants had stomachache with 25 mg oral prednisolone daily, which led to discontinue the trial [27]. Moreover, transient hyperglycemia was reported in the study by Shabana et al. that resolved spontaneously by stopping the methylprednisolone consumption [19]. It is worth mentioning that asthenia was the most prevalent side effect of phloroglucinol-added MET [11]. In addition, three patients in combination MET with nifedipine were stopped the treatment due to headache, heart palpitation and perimalleolar edema, which presumed was related to the nifedipine.

Discussion

Ureteral wall spasms caused by obstructing stones can interfere with successful stone passage. Significant inflammatory reaction with mucosal edema is common at the level of ureteral stone that may obstruct the ureteral lumen even with small stones leading to subsequent complications [16]. In the recent years, there has been a paradigm shift in the use of medical treatments to decrease ureteral peristaltic contractions while maintaining its tonic activities, which would allow distal propulsion of the stone [12, 17]. In the current NMA, we assessed the efficacy of different combination MET compared to α-blockers alone or each other. Our results revealed that combination MET with α-blockers, PDE5-Is, corticosteroids and phytotherapy increased the rate of SER 2.7 to 3.1 times more than α-blockers alone. Moreover, combination of nifedipine + corticosteroids seem more effective than corticosteroids alone. Regarding the expulsion time, statistically significant decrease in SET was found in combination of α-blockers and PDE5-Is compared to α-blockers alone or monotherapy groups.

Table 3 Summary of the results of network meta-analysis for the secondary outcomes including stone expulsion time (the left lower triangle) and mean analgesia use (the right upper triangle). Bold numbers indicate statistically significant results ($p < 0.05$)

Network meta-analysis of mean analgesia use								
α-blocs	0.2(-0.3,0.6)	**1.0(0.4,1.7)**	NA	0.7(-0.1,1.6)	NA	**-1.1(-1.9,-0.3)**	**1.2(0.4,1.9)**	NA	**-1.7(-2.5,-0.9)**
-0.1(-5.7,5.5)	α-blocs + Steroids	**0.9(0.1,1.7)**	0.6(-0.1,1.2)	**-1.3(-1.9,-0.6)**	NA	NA	**1.0(0.5,1.6)**	NA	**-1.8(-2.5,-1.2)**
-3.8(-7.0,-0.5)	-3.6(-10.2,2.8)	α-blocs + PD5-Is	NA	-0.3(-1.3,0.7)	NA	**-2.2(-3.2,-1.1)**	0.1(-0.8,1.1)	NA	**-2.7(-3.8,-1.7)**
-3.4(-7.2,0.3)	-3.3(-9.7,3.1)	0.3(-4.6,5.3)	α-blocs + Phyto	NA	NA	NA	NA	NA	NA
-0.6(-8.0,6.8)	-0.5(-13,4.3)	3.1(-4.9,11.2)	2.8(-5.3,10.8)	Misc Com*	NA	**-1.9(-2.8,-0.9)**	0.4(-0.2,1.1)	NA	**-2.4(-3.4,-1.5)**
5.2(-4.6,15.1)	5.3(-2.7,13.4)	9.0(-1.3,19.4)	8.6(-1.7,18.9)	5.8(-2.2, 13.9)	Steroids	NA	NA	NA	NA
4.0(-2.0,10)	4.1(-1.3,9.6)	**7.8(1,14.6)**	7.4(1.0,13.8)	4.6(-2.6,11.9)	-1.2(-11,8.5)	Misc Mono**	**2.3(1.4,3.2)**	NA	**-0.5(-1.5,0.4)**
0.6(-7.6,8.9)	0.7(-5.2,6.7)	4.4(-4.4,13.3)	4.0(-4.7,12.9)	1.2(-4.7,7.2)	-4.6(-10,0.8)	-3.4(-11.5,4.7)	Nif + Steroids	NA	**-2.8(-3.7,-1.9)**
0.9(-4.8,6.7)	1.0(-7.0,9.1)	4.7(-1.0,10.5)	4.3(-2.5,11.2)	1.5(-7.8,10.9)	-4.3(-15.7,7.1)	-3.1(-11.4,5.2)	0.3(-9.7,10.4)	PD5-Is	NA
5.0(-3.5,13.5)	5.1(-1.2,11.4)	8.7(-0.3,17.9)	8.4(-0.6,17.4)	5.6(-2.3,13.5)	-0.2(-10.5,10.0)	1.0(-7.4,9.4)	4.3(-4.4,13.1)	4.0(-6.2,14.3)	Wait
Network meta-analysis of stone expulsion time									

Data are the mean difference (MD) and 95% confidence interval. The row-defining drug intervention is compared with the column-defining drug intervention

α-blocs. α-blockers, PDE5-Is. PDE-5 inhibitors, Steroids. Corticosteroids, Wait. Watchful waiting, α-blocs + PDE5-Is. α-blockers + PDE-5 inhibitors, α-blocs + Steroids. α-blockers + Corticosteroids, α-blocs + Phyto. α-blockers + Phytotherapy, Nif + Steroids. Nifedipine + Corticosteroids, Misc Com. Miscellaneous Combination therapy, Misc Mono. Miscellaneous Monotherapy

*Miscellaneous Combination groups included; Tamsulosin (0.4 mg/d.) + Tadalafil (10 mg/d.) + Prednisolone, Phloroglucinol (80 mg/TDS) + Deflazacort (30 mg/d.), Phloroglucinol (80 mg/TDS) + Deflazacort (30 mg/d.), Tamsulosin (0.4 mg/d.) + Deflazacort (24 mg/d.) + Furosemide (40 mg/d.), and Tamsulosin (0.4 mg/d.) + Furosemide (40 mg/d.), **Miscellaneous monotherapy groups included; Rowatinex, Ketorolac, and Furosemide

Finally, significantly less analgesia use was seen in the combination of α-blockers and PDE5-Is when compared to α-blockers and corticosteroids or α-blockers alone. In addition, combined nifedipine with corticosteroids showed significantly less MAU compared to α-blockers alone, α-blockers with corticosteroids, and monotherapy groups.

Given the high density of α1-adrenergic receptors in the distal ureter, different α-blockers with different uroselectivity have been used with the impression of inhibiting basal smooth muscle contraction and uncoordinated hyperperistaltic spasms, while maintaining intra-ureteral pressure gradient around the stone. Alfuzosin has no pharmacological uroselectivity while tamsulosin blocks the α-1 A and α1-D receptors, silodosin is highly selective for α-1 A receptor, and naftopidil has an effect on both α-1 A- and α-1D-receptors, but its affinity is approximately three-fold stronger for the α-1D-receptors than the α-1 A [2, 7, 16, 18, 27, 30–34]. While α1-D receptors are more abundant than α1-A, ureteral smooth muscle contraction predominantly relies on α1-A receptors, as evidenced by gene and protein expression profiles and contractile function analyses. This may explain why silodosin has demonstrated greater efficacy than tamsulosin for MET in the existing literature [18].

As mentioned earlier, PDE5-Is acts via the nitric oxide/cyclic guanosine monophosphate pathway, which leads to ureteral smooth muscle relaxation. Vardenafil is the most potent PDE5Is, and tadalafil is the least potent but more selective one [2, 10, 27, 32]. The concomitant use of PDE5-Is and α-blockers revealed better ureteral relaxation probably due to different pathways action on the ureteral smooth muscle contraction with significant pain control without adding significant side effects [3, 10]. In two studies by Kloner et el., the combination of tamsulosin and tadalafil was found to be safe [19, 20], as this was also shown in study by Bechara et al. [21]. Some studies reported that the prescription of tadalafil in patients with lower ureteric stone could provide another beneficial effect on improving erectile dysfunction when this problem coexists with ureteral stone [3]. In our NMA, combination MET of α-blockers and PDE5-Is had 2.7 more times higher SER together with significantly lower SET and analgesia use compared to α-blockers alone. Some patients had some degree of penile intumescence without any report of priapism [3, 10, 11, 15].

Early treatment with corticosteroids can result in decreasing the ureteral wall edema and inflammatory reactions at the site of stone impaction, which allows stone propulsion in the ureter [17, 22]. While some studies have demonstrated the benefit of combination MET with corticosteroids and α-blockers on SER [9, 23], the other clinical trials did not support this findings [17, 22]. Because of diversity in the prescribed steroid agents

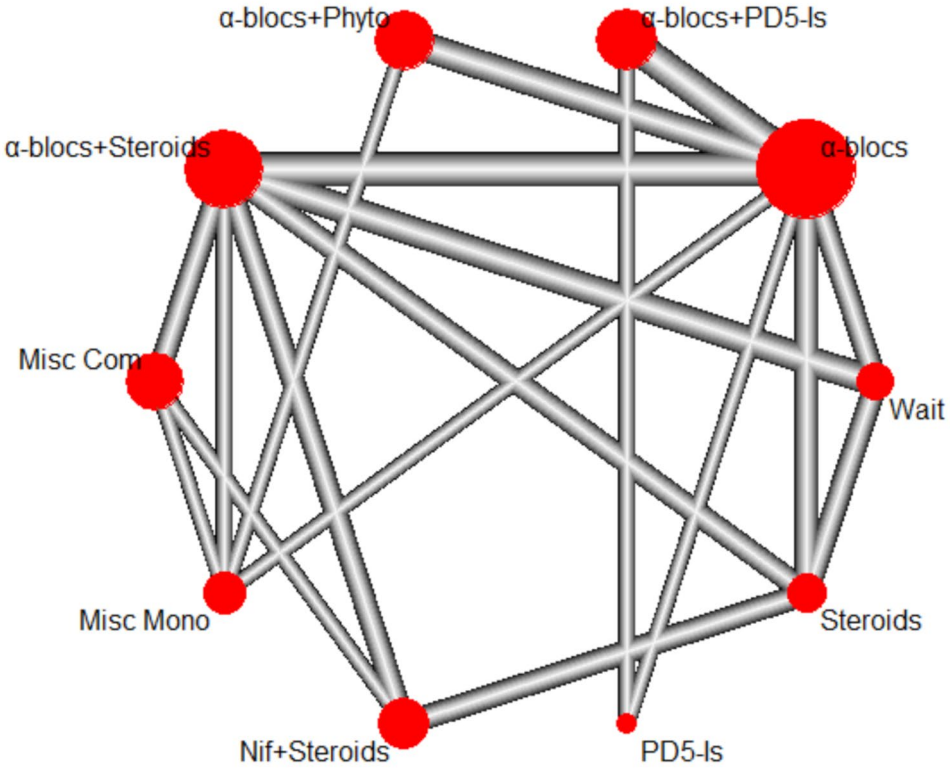

Fig. 3 Network plots for stone expulsion rate
α-blocs. α-blockers, PDE5-Is. PDE-5 inhibitors, Steroids. Corticosteroids, Wait. Watchful waiting, α-blocs + PDE5-Is. α-blockers + PDE-5 inhibitors, α-blocs + Steroids. α-blockers + Corticosteroids, α-blocs + Phyto. α-blockers + Phytotherapy, Nif + Steroids. Nifedipine + Corticosteroids, Misc Com. Miscellaneous Combination therapy, Misc Mono. Miscellaneous Monotherapy

[22, 24, 25], lack of standard dosing and duration of the treatment, the evidence remains inconclusive to recommend its routine prescription in MET [22, 23]. Our studies revealed that combination MET with α-blockers and corticosteroids could significantly increase the expulsion rate (2.73 times) without lowering the expulsion time or increasing analgesia use.

Smooth muscle contraction in most tissues typically results from increased intracellular calcium. Studies show that calcium channel blockers like nifedipine reduce fast electrical activity in ureteral tissue but do not affect the basic peristaltic rhythm [3, 26]. Although early research on nifedipine for ureteral stone passage exists, most studies indicate it is less effective than tamsulosin and associated with more adverse events. However, in this study, the combination of nifedipine and corticosteroids showed better outcomes in SER compared to some treatments (such as miscellaneous monotherapy and Steroids), did not differ significantly from others, and was less effective than α-blockers + corticosteroids (Table 2). According to Table 3, while it was not significantly different from other treatments in terms of MAU, it still performed better than α-blockers alone, α-blockers + corticosteroids and miscellaneous monotherapy.

Few studies evaluated the effects of phytotherapy in combination with α-blockers. Rowatinex is a compound drug containing seven natural terpenes including pinene (31%), camphene (15%), borneol (10%), anethole (4%), fenchone (4%), and cineole (3%) in olive oil and has been introduced as MET for kidney stone management in the literature [27]. Phloroglucinol (1,3,5-Trimethoxybenzene) is a synthetic agent with weak anticholinergic properties, which selectively acts on smooth muscle fibers in a state of spasm, which was used as monotherapy MET in some studies [13, 28]. Bromelain is another phytotherapy composed of a mixture of proteolytic enzymes extracted from pineapple (Ananas comosus). It is known for its anti-inflammatory, antimicrobic, antithrombotic and fibrinolytic effects [29]. In the current study, combination MET with phytotherapy and α-blockers resulted 3.1 higher SER compared to α-blockers alone without significant effect on reducing the expulsion time.

The effect of various other combination MET protocols was also investigated in our study and showed considerable results on SER, SET and MAU. For example, the combination MET with nifedipine and corticosteroids seemed more effective than corticosteroids alone or other monotherapy groups in lowering SER. Corticosteroids alone had lower efficacy in SER compared

to α-blockers alone. Expulsion time was significantly lower when α-blockers and PDE5-Is were compared to α-blockers alone or monotherapy with rowatinex, ketorolac or furosemide. Finally, analgesia use was significantly lower in α-blockers and PDE5-Is compared to α-blockers and corticosteroids or α-blockers alone.

Regarding the choice of combination therapy for distal ureteral stone passage, it seems that the use of α-blockers is recommended as an essential component because of its high specific effect on distal ureteral smooth muscle and low side effects as well as their supportive evidences in different combination groups. However, choosing the PDE5-Is, corticosteroids, or phytotherapy for combination with α-blockers should be individualized according to the patient's status, preferences and side effect profiles. For example, corticosteroids have received increased attention as a potential useful adjunct in first week of MET [9], however, their side effects should be considered. PDE5-Is could be a reasonable choice, especially in patients with simultaneous erectile dysfunction, and phytotherapy can be based on patient's preference. Combination nifedipine or diuretics with α-blockers require further investigation based on our understanding of the current data.

It is worth mentioning that MET for ureteral stones has become controversial due to conflicting results from recent high-quality trials and meta-analyses. While guidelines and reviews support MET, robust randomized clinical trials often show minimal evidence of benefit. These discrepancies may arise from broad inclusion criteria or insufficient power for subgroup analyses, highlighting the need for detailed study evaluations [30–33].

One of the limitations of this network meta-analysis is the scarcity and inconsistency of the data on analgesic use in the primary studies. Some studies did not report about the type and dosage of consumed analgesic Moreover, various analgesic treatments with different doses have been prescribed to the patients in other studies, that it was not possible to include them for assessment of MAU analysis. The heterogeneity of the data made it difficult to compare and combine the results across the studies and to draw reliable conclusions about the effectiveness of the treatments. Second, a few included studies did not have enough descriptions regarding randomization, conceal allocation, and blinding, which may lead to synthetize unreliable evidence. And finally, we found only a limited number of studies include combination of nifedipine or phytotherapy agents with α-blockers or PDE5-Is.

Conclusions

In conclusion, combination MET increases SER, and decreases SET or MAU compared to monotherapy with α-blockers alone. The combination of α-blockers with PDE5-Is, corticosteroids, and phytotherapy increases the rate of SER about three times more than α-blockers alone. SET was significantly lower in α-blockers + PDE5-Is compared to α-blockers alone. Finally, the combination of α-blockers with PDE5-Is, and nifedipine with corticosteroids showed less MAU, significantly. Further studies are warranted to find the most effective and least harmful combination recipe for passage of ureteral stone.

Abbreviations

MET	Medical Expulsive Therapy
NMA	Network Meta-Analysis
SER	Stone Expulsion Rate
SET	Stone Expulsion Time
SWL	Shockwave lithotripsy
MAU	Mean Analgesia Use

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Author contributions

MT, AK and PZ contributed to the study conception and design. Searching the medical database and data collection was done by SN, SSh and YM. Conducting the study and writing the first draft of the manuscript was done by PZ and MT. Investigation process with main revision of the manuscript were performed by MT, HA, AK and NB. Application of statistical and mathematical or other formal techniques to analyze the study data was done by N.B. All authors read and approved the final manuscript.

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Data availability

Yes, The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The ethics committee of the Urology and Nephrology Research Center (Shahid Beheshti University of Medical Sciences, Tehran, Iran) approved the study protocol (IR. SBMU. UNRC.REC. 1402.004).

Consent for publication

Not applicable.

Clinical trial number

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Compliance with the Helsinki declaration

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Competing interests

The authors declare no competing interests.

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