A network meta-analysis on the beneficial effect of medical expulsive therapy after extracorporeal shock wave lithotripsy

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We applied a newly introduced method, network meta-analysis, to re-evaluate the expulsion effect of drugs including tamsulosin, doxazosin, nifedipine, terazosin and rowatinex after extracorporeal shock wave lithotripsy (ESWL) as described in the literature. A systematic search was performed in Medline, Embase and Cochrane Library for articles published before March 2016. Twenty-six studies with 2775 patients were included. The primary outcome was the number of patients with successful stone expulsion. The data were subdivided into three groups according to duration of follow-up. A standard network model was established in each subgroup. In 15-day follow-up results, SUCRA outcome showed the ranking of effects was: doxazosin > tamsulosin > rowatinex > nifedipine > terazosin (88.6, 77.4, 58.6, 32.2 and 30.4, respectively). In 45-day follow-up results, SUCRA ranking was: tamsulosin > nifedipine > rowatinex (69.4, 67.2 and 62.6, respectively). In 90-day follow-up results, SUCRA ranking was: doxazosin > rowatinex > tamsulosin (84.1, 68.1 and 49.1, respectively). In conclusion, doxazosin and tamsulosin have potential to be the first choice for pharmacological therapy to promote the expulsion of urinary stone fragments after ESWL, with this doxazosin can improve the SFR in the long term, while tamsulosin may result more in accelerating the process of expulsion.

Extracorporeal shock wave lithotripsy (ESWL) represents an effective minimally invasive treatment for renal and ureteral stones greater than 5 mm in size. However, the elimination of calculus disintegrated by ESWL depends on many factors, including stone fragment volume, location and renal collecting system anatomy, as well as ureteral status, such as oedema and spasm. To improve the results of ESWL, many institutions have combined medical expulsive therapy (MET) for urinary stone treatment to obtain a better stone-free rate (SFR).

Medications for urinary calculus such as α-adrenoceptor antagonist or calcium channel blocker have been investigated as spasmolytic agents that would promote the expulsion of stones. Among these, tamsulosin and nifedipine have received the most attention. Both tamsulosin and nifedipine are believed to act on the ureteral muscle, causing relaxation and dilation of the ureter and facilitating the elimination of fragments, while nifedipine also relaxes the ureteropelvic junction, improving the urine flow to the ureter. However, among the clinical data related to MET, contradictory results have been reported. Recently, Pickard and colleagues reported a high-quality randomized controlled trial, concluding that tamsulosin and nifedipine were not effective at decreasing the need for further treatment for patients compared with expectantly managed ureteric calculus. Thus, whether MET can improve SFR after ESWL also requires re-evaluation.

Several randomized controlled trials (RCTs) studying the SFRs in different types of pharmacological therapy after ESWL have been reported. However, most of these studies were designed to compare the clearance rates...
between one medication and control\textsuperscript{8–10,12,13,15–20,22–32}. Moreover, in most studies, an arbitrary endpoint time was set to assess the stone clearance rate while ignoring possible variations of therapeutic effect before and after that endpoint time\textsuperscript{8–14,18,19,21,23,25,26,28,29,31–33}. Accordingly, one RCT can precisely resolve the issue of whether a medication can improve the SFR compared with a placebo or watchful waiting after a certain period, but cannot provide a wide view of its expulsion effect throughout the therapeutic process, and cannot reveal the difference between medications either.

In this context, network meta-analysis is a useful method in which multiple treatments can be directly or indirectly compared even if they are not designed in the same RCT, but have the same control group\textsuperscript{34,35}. In the current study, this approach was used to examine available RCTs to again explore the efficacy of pharmacological therapies including tamsulosin, doxazosin, nifedipine, terazosin and rowatinex in promoting the expulsion of urinary stone fragments after ESWL. More importantly, we subdivided the available data according to follow-up duration, and then compared whether there were differences between those medications throughout the period of stone expulsion.

**Materials and Methods**

The present systematic review was performed in accordance with the latest Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement\textsuperscript{36}.

**Search strategy and selection criteria.** We searched the US National Library of Medicine’s life science database (Medline), Embase, the Cochrane Central Register of Controlled Trials and the Cochrane Database for Systematic Reviews for articles published before March 2016. The language of publication was limited to English. Any of the terms ‘calcium-channel blocker’, ‘adrenergic alpha-antagonist’, ‘prostaglandin antagonist’, ‘prostaglandin’, ‘cortisone’, ‘nifedipine’, ‘verapamil’, ‘diltiazem’, ‘tamsulosin’, ‘terazosin’, ‘doxazosin’, ‘alfuzosin’, ‘prazosin’, ‘deflazacort’, ‘prednisone’, ‘medical therapy’, ‘drug therapy combination’, ‘medical management’, ‘expulsive therapy’, ‘facilitated passage’ and ‘adjunctive medical expulsive therapy’ was used in conjunction with any of the terms ‘urolithiasis’, ‘lithotripsy’, ‘extracorporeal shock wave lithotripsy’, ‘renal’, ‘urinary’ and ‘ureteral’. And the terms of ‘randomized controlled trial’ or ‘random’ was imposed as a restriction to the searching process. The search flowchart is presented in Fig. 1\textsuperscript{8–33}.

Studies that met all of the following criteria were included: (1) randomized controlled trials on the medical therapy for patients undergoing ESWL for renal or ureteral calculus; (2) studies reported the SFR and duration of follow-up; (3) after stone expulsion or at the end of the follow-up period, radiologic evaluation was mandatory to confirm stone passage; and (4) loss of follow-up rate \(<10\%\). Moreover, (5) crossover trials, dose titration studies, daily dosing studies and studies that were only available as abstracts were excluded.

**Outcome measures and data extraction.** The data were extracted by two independent reviewers (Yang and Chen). A third reviewer resolved any disagreements (Liao). We extracted trial design; trial size; details of intervention including dose and treatment duration; and patient characteristics such as mean age, sex, mean duration of symptoms, duration of follow-up, type of outcome (number of patients with successful stone expulsion) and outcome data at each duration of follow-up.
Table 1. Characteristics of included studies which the durations of follow-up were less than or equal to 15 days. Stone size and SWL sessions was presented as the mean or range value. Pts = patients; SWL = shock wave lithotripsy; SFRs = stone-free rates; NA = not available.

| Author, year | Pts(n) | research region | Gender (male, n) | Age (years) | Stone location | Stone size, mm | SWL sessions | Treatment | SFRs, % | Follow-up |
|--------------|--------|----------------|-----------------|-------------|----------------|---------------|--------------|-----------|---------|-----------|
| Ateş, 2012   | 35/44  | Turkey         | 25/33           | 38.4/31.0   | Upper ureteral | 9.06/8.30     | 1.26/1.23    | Doxazosin 4 mg/ non-Placebo | 94/80   | 2 weeks   |
| Romics, 2011  | 106/98 | Germany        | 62/53           | 51/48       | Renal          | 3–20          | 1/1          | Rowatinex 300 mg/ Placebo   | 21/14   | 1 weeks   |
| Hussein, 2010 | 67/69  | Egypt          | 40/45           | 44/40       | Renal          | 4–24          | 1–2          | Tamsulosin 0.4 mg/ non-Placebo | 15/12   | 2 weeks   |
| Wang, 2010    | 55/52  | China          | NA              | 42.2/40.9   | Lower ureteral | 9.3/8.6       | 1/1          | Tamsulosin 0.4 mg/ Placebo   | 75/46   | 2 weeks   |
| Djaladat, 2009| 50/50  | Iran           | 30/29           | 38.3/40.9   | Renal          | 10–20         | 1/1          | Rowatinex 300 mg/ Placebo   | 18/4    | 2 weeks   |
| Wang, 2009    | 34/35/38 | China       | 22/22/25        | 50.9/51.5/51.9 | Lower ureteral | 6.6/6.4/6.7    | 1/1/1        | Tamsulosin 0.4 mg/ Placebo   | 85/80/82 | 2 weeks   |
| Agarwal, 2009 | 20/20  | India          | 15/16           | 32.4/35.5   | Upper ureteral | 9.4/10.4      | 1.6/2.0      | Tamsulosin 0.4 mg/ non-Placebo | 55/25   | 15 days   |
| Choi, 2008    | 32/31/33 | Korea        | 25/26/25        | 48.0/45.2/45.9 | Ureteral     | 7.6/7.3/7.4    | 1/1/1        | Tamsulosin 0.2 mg/ Nifedipine 30 mg/ non-Placebo | 84/68/61 | 2 weeks   |
| Gravas, 2007  | 30/31  | Greece         | 18/20           | 48.8/49.2   | Distal ureteral | 8.3/8.5       | 1/1          | Tamsulosin 0.4 mg/ non-Placebo | 53/45   | 2 weeks   |
| Kupeli, 2004  | 24/24  | Turkey         | NA              | 42.7/43.1   | Lower ureteral | 8.2/8.6       | 1/1          | Tamsulosin 0.4 mg/ non-Placebo | 71/33   | 15 days   |

Risk of bias assessment. Two review authors (Yang and Chen) independently evaluated all relevant clinical studies for methodological quality. Each review author performed this assessment using The Cochrane Collaboration’s Risk of Bias tool, which included quality of random allocation concealment, description of dropout and withdrawal, intention-to-treat analysis, and blinding procedures for treatment and outcome assessments. A third reviewer resolved any disagreements by discussion (Liao). We synthesized qualitative information using Review Manager, version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, http://tech.cochrane.org/revman).

Statistical analysis. The primary outcome was the number of patients with successful stone expulsion before the time point of interest. We subdivided the outcome data into three groups according to the duration of follow-up as follows: ≤15 days (group 1); >15 but ≤45 days (group 2); and >45 but ≤90 days (group 3).

The final analysis here included 26 studies with 5 interventions (tamsulosin, terazosin, doxazosin, nifedipine and rowatinex) compared with placebo or non-placebo on a total of 2775 patients. Ten studies reported expulsion results with follow-up duration ≤15 days (Table 1), for 16 studies the follow-up duration was >15 but ≤45 days (Table 2), and for 10 studies it was >45 but ≤90 days (Table 3). The details of the risk of bias are shown in Fig. 2.

The average SFRs for the included studies in group 1, 2 and 3 were 43.5%, 59.2% and 75.9%, respectively. The intervention studied by most trials was tamsulosin with 21 studies of 1025 patients, while doxazosin, nifedipine, terazosin and rowatinex were examined in 3 studies of 137 patients, 3 studies of 106 patients, 1 study of 35 patients and 2 studies of 156 patients, respectively. Placebo was employed in 7 studies of 439 patients, while the other 19 studies of 877 patients had a non-placebo control.

The average SFRs for placebo in group 1, 2 and 3 were 29.8%, 43.5% and 54.4%, while those for non-placebo were 40.7%, 57.0% and 72.6%, respectively. As for each medical therapy, the average SFRs for tamsulosin were 57.6%, 72.1% and 84.8%, while those for rowatinex were 19.9%, 37.8% and 67.9% in the same groups, respectively.

The results for terazosin in group 2 and 3, doxazosin in group 2, and nifedipine in group 3 were not available, so only the available results were analysed. Terazosin had an average SFR of 80% in group 1, doxazosin had ones of 94.3% and 91.2% in group 1 and 3, and nifedipine had ones of 67.7% and 62.7% in group 1 and 2, respectively.
A preliminary network meta-analysis was conducted among tamsulosin, placebo and non-placebo interventions without subdivision according to the time point of interest, to determine whether the placebo and non-placebo interventions could be pooled together. The results showed that there was no significant difference between placebo and non-placebo ($p > 0.05$). The SUCRA ranking was: tamsulosin > placebo > non-placebo (99.4, 0.6 and 0, respectively). Then, the following analyses were conducted using a control group that consisted of the placebo and non-placebo interventions.

The network meta-analyses were conducted in each subgroup. In group 1, doxazosin had the highest SUCRA rank which was the first possibility to be effective; however, its mean difference was not statistically significant when compared with control ($p > 0.05$), since a relative small number of patients were included in doxazosin intervention resulting in a relative large scale of 95% CI. Tamsulosin and rowatinex had the second and third SUCRA rank and their mean difference were statistically significant when compared with control ($p < 0.05$). Terazosin and nifedipine had lowest SUCRA rank which were the least likely to be effective. The SUCRA outcome showed the following efficacy ranking: doxazosin > tamsulosin > rowatinex > nifedipine > terazosin > control (Fig. 3).

In group 2, all involved interventions (tamsulosin, nifedipine and rowatinex) had SFRs that were significantly better than that in the control group ($p < 0.05$). They had almost the same SUCRA rank with similar possibility to be effective (Fig. 4).

In group 3, all involved interventions (tamsulosin, doxazosin and rowatinex) were associated with significantly better outcomes compared with control ($p < 0.05$). Doxazosin had the highest SUCRA rank which was the first

| Author, year | Pts(n) | Gender (male, n) | Age (years) | Stone location | Stone size, mm | SWL sessions | Treatment | SFRs, % | Follow-up |
|--------------|--------|-----------------|-------------|----------------|---------------|--------------|-----------|---------|-----------|
| Mohamed, 2013 | 65/65 | Egypt | 41/39 | Ureteral | 5–15 | 1–3 | Tamsulosin 0.4 mg/non-Placebo | 85/89 | 30 days |
| Park, 2013 | 44/44 | Korea | 29/28 | Proximal ureteral | 9.2/9.6 | 1/1 | Tamsulosin 0.2 mg/non-Placebo | 84/66 | 3 weeks |
| Elkoushy, 2012 | 63/63 | Egypt | 44/39 | Renal and upper ureteral | 11.1/10.5 | 1.5/1.9 | Tamsulosin 0.4 mg/non-Placebo | 55/46 | 3 weeks |
| Georgiev, 2011 | 99/87 | Bulgaria | 67/54 | Renal and ureteral | 5–20 | 1–2 | Tamsulosin 0.4 mg/non-Placebo | 74/56 | 4 weeks |
| Romics, 2011 | 106/98 | Germany | 62/53 | Renal | 3–20 | 1/1 | Tamsulosin 0.2 mg Placebo | 44/30 | 4 weeks |
| Singh, 2011 | 59/58 | India | 44/41 | Upper ureteral | 6–15 | 1/2 | Tamsulosin 0.4 mg/non-Placebo | 85/71 | 1 months |
| Vicentini, 2011 | 38/35/38 | Brazil | 16/18/24 | Renal | 10/10/12 | 1/1/1 | Tamsulosin 0.4 mg/ Nifedipine 20 mg/Placebo | 61/49/37 | 30 days |
| Hussein, 2010 | 67/69 | Egypt | 40/45 | Renal | 4–24 | 1–2 | Tamsulosin 0.4 mg/non-Placebo | 46/32 | 1 months |
| Djaladat, 2009 | 50/50 | Iran | 30/29 | Renal | 10–20 | 1/1 | Rowatinex 300 mg/Placebo | 24/18 | 4 weeks |
| Kobayashi, 2008 | 38/34 | Japan | NA | Ureteral | 10.61/9.85 | 1/1 | Tamsulosin 0.2 mg/non-Placebo | 84/88 | 28 days |
| Naja, 2008 | 51/65 | India | 36/43 | Renal | 12.1/13.1 | 1.66/2.16 | Tamsulosin 0.4 mg/non-Placebo | 53/31 | 3 weeks |
| Bhagat, 2007 | 29/29 | America | 22/24 | Renal and ureteral | 6–24 | 1/1 | Tamsulosin 0.4 mg/Placebo | 97/79 | 30 days |
| Gravas, 2007 | 30/31 | Greece | 18/20 | Distal ureteral | 8.3/8.5 | 1/1 | Tamsulosin 0.4 mg/non-Placebo | 63/52 | 4 weeks |
| Resim, 2005 | 32/35 | Turkey | 21/22 | Lower ureteral | 21/20 | N/A | Tamsulosin 0.4 mg/non-Placebo | 75/66 | 6 weeks |
| Gravina, 2005 | 65/65 | Italy | 28/29 | Renal | 14.2/14.6 | 1/1 | Tamsulosin 0.4 mg/non-Placebo | 55/46 | 4 weeks |
| Porpiglia, 2002 | 40/40 | Italy | 27/25 | Ureteral | 11.6/10.1 | 1/1 | Nifedipine 30 mg/non-Placebo | 75/50 | 45 days |

Table 2. Characteristics of included studies which the durations of follow-up were greater than 15 days but less than or equal to 45 days. Stone size and SWL sessions was presented as the mean or range value. Pts = patients; SWL = shock wave lithotripsy; SFRs = stone-free rates; NA = not available.
possibility to be effective; rowatinex and tamsulosin had the second and third SUCRA rank indicating that they were less likely to be effective compared with doxazosin. The SUCRA ranking was: doxazosin > rowatinex > tamsulosin > control (Fig. 5).

| Author, year | Pts(n) | research region | Gender (male, n) | Age(years) | Stone location | Stone size, mm | SWL sessions | Treatment | SFRs, % | Follow-up |
|--------------|-------|----------------|-----------------|------------|----------------|----------------|--------------|-----------|---------|-----------|
| Qadri, 2014  | 60/60 | Pakistan       | 41/48           | 39/41      | Renal          | 11.2/10.5      | 1/1          | Tamsulosin 0.4 mg/non-Placebo | 97/80    | 8 weeks   |
| Zaytoun, 2012| 50/50 | France         | 25/31/23        | 39.4/39.2/40.5 | Renal          | 16.6/16.1/15.9 | 2.02/2.12/2.08 | Tamsulosin 0.4 mg/ Doxazosin 4 mg/non-Placebo | 92/90/84 | 3 months |
| Georgiev, 2011 | 99/87 | Bulgaria       | 67/54           | 54/51      | Renal and ureteral | 5–20          | 1–2          | Tamsulosin 0.4 mg/non-Placebo | 91/75    | 12 weeks |
| Romics, 2011  | 106/98| Germany        | 62/53           | 51/48      | Renal          | 3–20           | 1/1          | Rowatinex 300 mg/ Placebo | 68/50    | 12 weeks |
| Singh, 2011   | 59/58 | India          | 44/41           | 32.2/36.0  | Upper ureteral | 6–15           | 1/2          | Tamsulosin 0.4 mg/non-Placebo | 92/86    | 3 months |
| Falahatkar, 2011 | 70/71 | Iran           | 53/52           | 45.5/47.0  | Renal and ureteral | 13.22/12.88   | 1/1          | Tamsulosin 0.4 mg/Placebo | 71/61    | 12 weeks |
| Hussein, 2010  | 67/69 | Egypt          | 40/45           | 44/40      | Renal          | 4–24           | 1–2          | Tamsulosin 0.4 mg/non-Placebo | 73/55    | 3 months |
| Alsagheer, 2008 | 52/53 | Egypt          | NA              | 35.2/33.6  | Renal and upper ureteral | 5–20          | 1–4          | Doxazosin 1 mg/non-Placebo | 92/75    | 12 weeks |
| Naja, 2008    | 51/65 | India          | 36/43           | 37.1/39.4  | Renal          | 12.1/13.1      | 1.66/2.16    | Tamsulosin 0.4 mg/non-Placebo | 94/85    | 12 weeks |
| Gravina, 2005 | 65/65 | Italy          | 28/29           | 48.4/47.9  | Renal          | 14.2/14.6      | 1/1          | Tamsulosin 0.4 mg/non-Placebo | 78/60    | 12 weeks |

Table 3. Characteristics of included studies which the durations of follow-up were greater than 45 days but less than or equal to 90 days. Stone size and SWL sessions was presented as the mean or range value. Pts = patients; SWL = shock wave lithotripsy; SFRs = stone-free rates; NA = not available.

Figure 2. Risk-of-bias analysis: (A) Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies. (B) Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.
The risk bias was low in all of the above network meta-analyses ($\tau^2 < 0.001$). No consistency problems were detected in this model (Appendix 3).

**Discussion**

Overcoming the absence of head-to-head comparisons between pharmacological therapies in promoting the expulsion of urinary stone fragments after ESWL in existing studies, our network meta-analysis of 26 RCTs provides evidence for the efficacy of commonly used medications for improving SFR after ESWL. Among these, doxazosin showed a superior recommendation level (SUCRA rank) over all other medications at the follow-up durations of $\leq 15$ days and $45–90$ days. Doxazosin has the potential to be considered as the first choice of pharmacological therapy for improving SFR after ESWL. Unfortunately, the effect of doxazosin at time point of $15–45$ days was not assessed because of a lack of available data for statistical analysis. Tamsulosin and rowatinex were shown to be effective for improving SFR after ESWL at all three time points, but the results did not support tamsulosin or rowatinex as the best choice due to relatively low recommendation levels. In addition, tamsulosin seemed to have a decreased trend of efficacy over the duration of follow-up; its SUCRA score dropped from 77.4 at 15 days to 49.1 at 90 days, which represented a change from being higher than that of rowatinex to being lower than it. Nifedipine did not show effectiveness at a time point of less than 15 days, but could improve the SFR after ESWL at 45 days, almost the same as tamsulosin, indicating that the relaxation and dilation effects of nifedipine on ureteral smooth muscle were slow. Terazosin did not show effectiveness at a follow-up duration of less than 15 days with only one included RCT, which studied lower ureteral stone MFT after ESWL. As a pharmacological therapy for upper ureteral or renal stone fragments after ESWL, the efficacy of terazosin is unknown.
These results provide a very wide perspective about the expulsion of stone fragments after ESWL with or without medications. Normally, stone fragments generated by ESWL are smaller than 4 mm and tend to pass spontaneously through the ureter without the influence of any drug. The fragment size is an important factor that determines the passage of a stone through the narrowest part of the ureter. If the stone fragments are slightly larger, then the expulsion is often accompanied by colic and lower urinary tract symptoms, sometimes lasting several days, which cause discomfort. If the stone fragments are larger than 6 mm, or any ureteral status such as edema or spasm occurs, the fragments may not pass the ureter and repeat treatment or a secondary procedure will be needed. For the two hypothetical conditions above, MET after ESWL provides two possible sources of efficacy: accelerating the process of expulsion or improving the SFR.

A single RCT often focuses on the effectiveness of one or two medications within a certain period. According to its design, it can precisely resolve the issue of whether these medications can improve the SFR compared with a placebo or watchful waiting. However, what if a medication can only accelerate the process of expulsion in a short period such as 15 days, but does not improve the SFR in a long period such as 30 days or more? In this case, an analysis for a short time will lead to the conclusion that the medication worked, but an analysis at the end will result in the conclusion that it was useless. Pickard and colleagues used the double-blind, randomized, controlled procedure will be needed. For the two hypothetical conditions above, MET after ESWL provides two possible sources of efficacy: accelerating the process of expulsion or improving the SFR.

Selective α1-adrenoceptor antagonist has a certain rapid effect for promoting the expulsion of stone fragments. It is well established that the density of α1-adrenoceptors is higher in the distal ureter. Studies have also shown that tamsulosin acts on α1A and α1D receptors in the lower ureter, prevents spasm by relaxing the smooth muscle of the ureter, reduces proximal ureteral pressure and acts on the C-fibres blocking pain conduction. Moreover, Tamsulosin has little effect on blood pressure, while doxazosin and terazosin can lead to orthostatic hypotension; this is because tamsulosin is highly selective for the α1A receptor, which is specifically located in the urinary system, while doxazosin and terazosin have low selectivity for α1-adrenoceptor subtypes. The current study demonstrated that doxazosin had a higher SUCRA score than tamsulosin for improving SFR after ESWL. A possible hypothesis to explain this is that high selectivity on α1-adrenoceptor subtypes of tamsulosin may result in lower efficacy of blocking than subtypes of doxazosin with low selectivity. Our data indicate that doxazosin can improve the SFR after ESWL, while tamsulosin may result more in acceleration of the process of expulsion after ESWL. This is because the SUCRA rank of tamsulosin dropped from 77.4 at 15 days to 49.1 at 90 days, indicating that more stone fragments may be passed spontaneously in the long term without the influence of medication. Our data also demonstrated that terazosin had no impact on improving SFR after ESWL at 15 days; however, more well-designed RCTs should be performed to investigate the efficacy and safety of doxazosin and terazosin for promoting the expulsion of stone fragments.

Calcium channel blockers have also received wide attention for their efficacy at promoting the expulsion of urinary stones, because smooth muscle contraction is directly caused by an increase in calcium concentration. Nifedipine also relaxes the ureter, leading to less pain, but Davenport and colleagues performed an interesting study showing that nifedipine could not reduce the contraction frequency of the ureter and could not maintain ureteric pressure at a relatively low level as well as tamsulosin could. The current consensus is that nifedipine...
has an effect of promoting the expulsion of ureteral stones but is not superior to tamsulosin, either in improving SFR or in reducing expulsion time. Our data confirmed that nifedipine could not improve the SFR after ESWL at a follow-up duration of less than 15 days, but was effective upon drug therapy for more than 30 days. This indicated that the relaxing and dilatory effects of nifedipine on ureteral smooth muscle occurred later than for α-adrenoceptor antagonist, meaning that nifedipine may have less potential to reduce the discomfort of patients who are suffering ureteral calculus compared with tamsulosin.

Rowatinex is an essential oil preparation of terpene composed of pinene (3%), camphene (15%), borneol (10%), anethol (4%) and cineol (3%) in olive oil, which has been suggested for the treatment of urolithiasis and other urological problems. It was assumed to improve renal blood flow, thus giving rise to increased urine excretion, and to have antispasmodic effects to facilitate the passage of urinary stones. In contrast to other medications, the mechanism of rowatinex for promoting the expulsion of stone fragments is a combined effect and cannot be clearly outlined; nevertheless, clinical data showed that it is not only a valuable drug used for urolithiasis, but also has spasmylocytic and anti-inflammatory properties. The current study demonstrated that rowatinex had a relatively stable SUCRA score from 1-week to 12-week follow-up after ESWL. It was even better than tamsulosin at the time point of 90 days after ESWL, but more studies are needed to investigate that effectiveness further.

Some limitations of the present network meta-analysis should be mentioned: (1) The outcome data were subdivided into three groups according to the follow-up duration with the intent of exploring the effect of these medications over time. However, there were no data for terazosin at 45 and 90 days, doxazosin at 45 days and nifedipine at 90 days after ESWL in the existing literature. Hence, the conclusion that doxazosin has potential to be the first choice or to be better than other medications for improving SFR after ESWL still requires more well-designed RCTs to be confirmed. In addition, the long-term efficacy of nifedipine or terazosin as MET after ESWL is still unclear. (2) Among 2775 patients in 26 RCTs that we included, 1025 patients in 21 RCTs were assigned to tamsulosin intervention, while only limited studies focused on doxazosin, nifedipine, terazosin and rowatinex, with only 137 patients in 3 RCTs, 106 patients in 3 RCTs, 35 patients in 1 RCT and 156 patients in 2 RCTs, respectively. Thus, because of the weight relationship in network meta-analysis, the outcome of interventions with very few objects may be affected by calculating with an intervention with vast objects through the network meta-analysis model. Therefore, more studies are needed before a definitive conclusion about the effect of MET after ESWL can be drawn. (3) Although no problems with consistency were detected here, the SFR ranged from 4% to 89% in the control group and from 15% to 97% under medical interventions. The reason for this was that cases with a wide range of locations of stones from the kidney to the distal ureter were included, and different criteria regarding how stone clearance was defined were used in different studies. Thus, a potential for bias may have been generated.

Conclusion

The current network meta-analysis demonstrated that tamsulosin, doxazosin, nifedipine and rowatinex are effective for promoting the expulsion of urinary stone fragments after ESWL, of which α-adrenoceptor antagonists are better than calcium channel blockers, especially at a short expulsion time. Among three types of α-adrenoceptor antagonists, doxazosin can improve the SFR after ESWL in the long term, while tamsulosin may result more in accelerating the process of expulsion after ESWL, but terazosin did not show any efficacy, at least in the existing literature. Therefore, doxazosin and tamsulosin have the potential to be considered as the first choices of pharmacological therapy to improve SFR after ESWL, although more high-quality RCTs will be needed to evaluate the efficacy and reliability of doxazosin compared with tamsulosin.

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