**Systematic review and meta-analysis of the adjuvant role of Medical Expulsive Therapy (MET) in Shock Wave Lithotripsy (SWL) treatment of upper urinary stones**

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⁶ Private Practice, Athens, Greece.
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**Abstract**

**Introduction:** Medical expulsion therapy (MET) has been introduced as a method enhancing the spontaneous passage of stones and reducing the stone expulsion time after extracorporeal shockwave lithotripsy (SWL). The aim of the current meta-analysis was to analyze the data of randomized studies on MET implemented following SWL for renal and ureteral stones.

**Materials and Methods:** A systematic literature search of CENTRAL, WEB OF SCIENCE, PUBMED and SCOPUS was performed. The criteria applied for the selection of the included studies were: randomized, placebo or other comparator (i.e analgesics) controlled studies dealing with renal or ureteral stones treated with SWL and MET (including plant extracts) with a minimum...
Introduction

Urolithiasis is a common disease of the urinary tract. The prevalence ranges from 1 to 15% depending on age, gender, race and geographic location. Calculi located into the upper urinary tract may significantly affect patient’s quality of life and often different types of intervention are required to achieve a stone-free status \(^{[1,2]}\). Extracorporeal shock wave lithotripsy (SWL) has revolutionized the treatment of urinary stones in the 80’s and 90’s, initially replacing percutaneous lithotripsy which was actually invented prior to shock waves. Non-lower pole kidney stones of less than 20 mm in diameter, lower pole stones of less than 10 mm in diameter or up to 20 mm in diameter associated with favorable for SWL anatomy, and upper ureteral stones of less than 10 mm in diameter are the main indications for primary SWL treatment \(^{[1,2]}\). Still, residual fragments may constitute a significant problem to the patient. These fragments may remain unchanged and silent depending on their size, number and location in up to one third of the cases \(^{[3]}\). The rest will eventually increase in size and will be the cause of either pain or re-intervention. This is also true for those residuals less than 4mm in size which in the past were included under the term of “clinically insignificant fragments” \(^{[3]}\). The elimination of residual fragments may depend on various parameters such as their size, number and site, the anatomy of the calyx and the peristaltic capability of the upper urinary tract \(^{[3,4]}\). Medical expulsion therapy (MET) has been introduced as a method promoting the spontaneous passage of ureteral stones and reducing the stone expulsion time after lithotripsy. Pharmaceutical agents such as calcium channel blockers, corticosteroids, non-steroidal anti-inflammatory drugs and α-blockers have been investigated as methods to enhance the outcome of the SWL \(^{[1]}\).

The aim of the current meta-analysis is to evaluate the efficacy of MET, primary in the terms of improving stone-free rates and/or reducing stone expulsion time, after SWL for urinary stones.

Materials and Methods

Search strategy and study selection

We first conducted a search of CENTRAL, WORLD OF SCIENCE, PUBMED and SCOPUS using meticulously selected search terms and Boolean operators. The literature search was conducted independently by two groups of investigators (three investigators in each group) and it was restricted to human research studies. No limit was placed on language. Manual searches of references cited by the published original studies and review articles supplemented the database search strategy.

Article selection proceeded according to the search strategy based on Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria (www.prisma-statement.org; Figure 1). The criteria applied for the selection of the included studies were: randomized, placebo or other comparator (i.e analgesics) controlled studies, minimum follow-up of 14 days and studies dealing with renal or ureteral stones treated with SWL and MET (including plant extracts). The exclusion criteria were: non randomized-non comparative studies, follow-up period less than 14 days and bladder stones studies. The primary end-points of the analysis were: clearance (or success) rate (stone-free rate and/or residual fragments <4mm and/or asymptomatic residual frag-
Systematic review and meta-analysis of the adjuvant role of Medical Expulsive Therapy (MET) in Shock Wave Lithotripsy (SWL) treatment of upper urinary stones, p. 32-44

ments <4mm) and stone expulsion time, both stratified according to type of MET, stone size and stone location. Secondary end-points included the retreatment rate (SWL, ureteroscopy, percutaneous nephrolithotripsy), the number of patients needed to treat, the number of patients with colic episodes, the number of colics per patient, the need for analgesia prior to expulsion and the complication rate.

Statistical analysis

Quantitative data synthesis

Meta-analytic pooling was performed for each class of MET. The dichotomous data for each of the eligible studies were extracted in a 2x2 table and expressed as odds ratio (OR) with 95% confidence intervals (CI). When the outcome of interest was of a continuous nature (i.e. time to expulsion) the differences were pooled across the studies which provided information on this outcome, resulting in a weighted mean difference (WMD) with 95% CI. These results were combined for meta-analysis using the inverse variance method, when using the fixed effects model [5]. In the case of random effects model, the DerSimonian and Laird [6] method was used.

Study-to-study variation was assessed by using the Chi² statistical method. In addition, the use of the I² index was employed in order to indicate the proportion of inconsistency between studies that could not be attributed to chance, with I²≥50% indicating significant heterogeneity [7]. A fixed effects model was used where no statistically significant heterogeneity was present, whereas in the presence of significant heterogeneity as indicated either by the Chi² test or the I² index, a random effects model was applied. Statistical significance was set at a p level of 0.05.

The presence of publication bias was assessed by constructing and visually examining funnel plots, as well as by performing the Egger’s test [8,9]. All analyses were performed according to the per protocol and the intention-to-treat principle when there was a discrepancy between the patients randomized and those who were eventually analyzed in each paper. All results were combined for meta-analysis with the Review Manager [computer software] (RevMan, Version 5.2; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012).

Subgroup Analyses

Subgroup analyses were a priori planned to be performed depending on the: Type of α-blocker, size and location of stone.

Evidence synthesis

Characteristics of the included studies

The literature search yielded a total number of 1401 studies (Figure 1). The study selection process resulted in the inclusion of 26 articles. Most of the studies were published within the last 5 years reflecting the increased interest in the field. All corresponding authors of the studies were contacted and replied for missing or unclear data.

The clinical and treatment related characteristics of all included studies are presented in Table 1. The included studies were conducted in all continents. Thus, the results should be considered as the effect of MET in a variety of populations. 2884 patients were randomized in the included studies and received MET in combination to SWL.
1) Quantitative analysis for medical expulsive therapy and stone clearance at specific time points.

1.1) α-Blockers

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>MET Events</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atkins et al., 2012</td>
<td>33</td>
<td>35</td>
<td>68</td>
<td>5.2%</td>
<td>4.24 [0.85, 21.11]</td>
<td></td>
</tr>
<tr>
<td>Choi et al., 2008</td>
<td>27</td>
<td>32</td>
<td>59</td>
<td>9.0%</td>
<td>3.51 [0.88, 14.15]</td>
<td></td>
</tr>
<tr>
<td>Han et al., 2006</td>
<td>20</td>
<td>22</td>
<td>42</td>
<td>3.9%</td>
<td>5.33 [0.99, 28.84]</td>
<td></td>
</tr>
<tr>
<td>Hirasawa et al., 2012</td>
<td>33</td>
<td>40</td>
<td>73</td>
<td>11.8%</td>
<td>3.48 [1.25, 9.75]</td>
<td></td>
</tr>
<tr>
<td>Hussein et al., 2010</td>
<td>10</td>
<td>67</td>
<td>77</td>
<td>19.7%</td>
<td>1.34 [0.49, 3.53]</td>
<td></td>
</tr>
<tr>
<td>Kupeli et al., 2004</td>
<td>25</td>
<td>39</td>
<td>64</td>
<td>11.6%</td>
<td>4.53 [1.73, 11.53]</td>
<td></td>
</tr>
<tr>
<td>Wang et al., 2009 in Tamsulosin</td>
<td>29</td>
<td>34</td>
<td>63</td>
<td>8.8%</td>
<td>1.09 [0.23, 5.15]</td>
<td></td>
</tr>
<tr>
<td>Wang et al., 2009 in Tamsulosin</td>
<td>28</td>
<td>35</td>
<td>63</td>
<td>11.4%</td>
<td>1.07 [0.27, 4.24]</td>
<td></td>
</tr>
<tr>
<td>Wang et al., 2010</td>
<td>41</td>
<td>55</td>
<td>96</td>
<td>18.4%</td>
<td>3.42 [1.51, 7.72]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>359</strong></td>
<td><strong>338</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>2.80 [1.93, 4.05]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 246, Heterogeneity: Ch² = 7.25, df = 7 (P = 0.46); I² = 0%
Test for overall effect: Z = 5.45 (P < 0.0001)

Figure 2a. Forest plots of comparison: α-blocker versus control; outcome: stone clearance at approximately 2 weeks. M-H, Mantel-Haenszel test; CI, Confidence Interval; df, degree of freedom.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>MET Events</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhaag et al., 2007</td>
<td>28</td>
<td>29</td>
<td>57</td>
<td>1.9%</td>
<td>7.30 [0.82, 65.11]</td>
<td></td>
</tr>
<tr>
<td>Grivas et al., 2007</td>
<td>19</td>
<td>30</td>
<td>49</td>
<td>14.1%</td>
<td>1.62 [0.58, 4.51]</td>
<td></td>
</tr>
<tr>
<td>Hussein et al., 2010</td>
<td>31</td>
<td>67</td>
<td>98</td>
<td>28.4%</td>
<td>1.84 [0.92, 3.70]</td>
<td></td>
</tr>
<tr>
<td>Kobayashi et al., 2008</td>
<td>32</td>
<td>38</td>
<td>70</td>
<td>12.2%</td>
<td>0.71 [0.18, 2.77]</td>
<td></td>
</tr>
<tr>
<td>Mukhtarov et al., 2007</td>
<td>24</td>
<td>24</td>
<td>48</td>
<td>0.9%</td>
<td>12.60 [0.64, 24.94]</td>
<td></td>
</tr>
<tr>
<td>Singh et al., 2011a</td>
<td>50</td>
<td>59</td>
<td>109</td>
<td>15.4%</td>
<td>2.30 [0.93, 5.71]</td>
<td></td>
</tr>
<tr>
<td>Singh et al., 2011b</td>
<td>52</td>
<td>60</td>
<td>112</td>
<td>13.8%</td>
<td>2.63 [1.03, 6.69]</td>
<td></td>
</tr>
<tr>
<td>Vincenzi et al., 2011</td>
<td>23</td>
<td>38</td>
<td>61</td>
<td>13.5%</td>
<td>2.63 [1.04, 6.64]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>345</strong></td>
<td><strong>339</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>2.16 [1.51, 3.10]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 259, Heterogeneity: Ch² = 5.97, df = 7 (P = 0.54); I² = 0%
Test for overall effect: Z = 4.20 (P < 0.0001)

Figure 2b. Forest plots of comparison: α-blocker versus control; outcome: stone clearance at approximately 1 month. M-H, Mantel-Haenszel test; CI, Confidence Interval; df, degree of freedom.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>MET Events</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirasawa et al., 2012</td>
<td>36</td>
<td>40</td>
<td>76</td>
<td>13.1%</td>
<td>3.86 [1.12, 13.26]</td>
<td></td>
</tr>
<tr>
<td>Hussein et al., 2010</td>
<td>43</td>
<td>67</td>
<td>110</td>
<td>52.9%</td>
<td>2.67 [1.04, 4.11]</td>
<td></td>
</tr>
<tr>
<td>Naja et al., 2008</td>
<td>48</td>
<td>51</td>
<td>99</td>
<td>11.9%</td>
<td>5.22 [1.34, 19.09]</td>
<td></td>
</tr>
<tr>
<td>Singh et al., 2011a</td>
<td>53</td>
<td>59</td>
<td>112</td>
<td>22.1%</td>
<td>2.30 [0.80, 6.63]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>217</strong></td>
<td><strong>232</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>2.73 [1.69, 4.40]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 180, Heterogeneity: Ch² = 1.98, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 4.12 (P < 0.0001)

Figure 2c. Forest plots of comparison: α-blocker versus control; outcome: stone clearance at approximately 2 months. M-H, Mantel-Haenszel test; CI, Confidence Interval; df, degree of freedom.

Stone clearance outcome was evaluated at approximately 2 weeks, 1 month, 2 months and 3 months. The number of studies and their respective patient popu-
lations that were analyzed at each time period are presented in Figures 2a, 2b, 2c, 2d. The analysis showed no heterogeneity, an overall benefit of stone expulsion at the above time periods and minor publication bias. The intention-to-treat analysis showed an overall benefit of the a-blockers at 2 weeks (OR: 2.77; 95% CI: 1.92–4.01) [10–17]. On the other hand, the intention-to-treat analysis demonstrated slightly worse results (OR: 1.97; 95% CI: 1.41–2.74) in comparison to the overall effect results at 1 month [18–25]. Similarly, the benefit of a-blockers was found to be smaller in the intention-to-treat analysis at 2 [13,14,23,26] and 3 months [14,22,23,26,27,28,29,30] (OR: 1.77; 95% CI: 1.19–2.63, OR: 1.71; 95% CI: 1.27–2.32, respectively) when compared to the overall effect.

1.2) Calcium channel blocker therapy

All three studies [11,25,31] investigating calcium-channel blockers used nifedipine for medical stone expulsion therapy (Figure 3). At ~2 weeks (14-15 days) and at ~1 month (28-31 days) no difference was detected between the patients who received nifedipine compared to control (OR: 1.36; 95% CI: 0.49–3.81 and OR: 1.62; 95% CI: 0.64–4.12, respectively). At ~ 45 days, a significantly increased probability of stone clearance was observed in patients who had received nifedipine (OR: 3.00; 95% CI: 1.16–7.73). Pooling of the three studies showed an increased probability of stone clearance with nifedipine as compared to the control (OR: 1.78; 95% CI: 1.03–3.07).

1.3) Rowatinex

Two studies [32,33] used Rowatinex for medical stone expulsion therapy after SWL. Stone clearance was significantly increased in patients who received Rowatinex as compared to patients who received placebo at ~2 weeks (14-15 days) (OR: 5.27; 95% CI: 1.08 - 25.78), at 1 month (28-31 days) (OR: 2.13; 95% CI: 1.28 - 3.56), at
2 months (56-62 days) (OR: 2.42; 95% CI: 1.32 - 4.43) and at 3 months (84-92 days) (OR: 3.95; 95% CI: 2.00 - 7.79). However, when the ITT analysis was performed, no statistically significant improvement was observed in the stone clearance rate at the 2 months time point (OR: 1.67, 95% CI: 0.96-2.91).

1.4) Choreito
Two studies [20,34] were analysed, including 213 patients (Figure 4). No heterogeneity was detected (P = 0.94; I² = 0%). Stone clearance was not significantly different at ~1 month (28-31 days) between choreito and the control group (OR: 1.27; 95% CI: 0.70–2.32).

1.5) Uriston
One trial [35] including 150 patients evaluated the efficacy of Uriston on stone expulsion. Stone clearance was significantly increased in the Uriston group at 1 month (OR: 4.83; 95% CI: 1.07–2.90) and at 2 months (OR: 4.23; 95% CI: 2.14–8.38). At the 3-month and 6-month time point, stone clearance appeared to be increased in the Uriston group in comparison to the control group. Nevertheless, this difference was not statistically significant (OR: 1.64; 95% CI: 0.81–3.30 and OR: 2.92; 95% CI: 0.97 – 8.75, respectively)
2) Quantitative analysis for stone clearance at specific time points per type of α-blocker

No significant difference in the stone clearance rate was detected between the different types of α-blocker at 2 weeks [10-17], 1 month [18,19,20,21,23,24,25] and 3 months [22,26,27,28,29,30] (p=0.51, p=0.07, p=0.44, respectively) (Figures 5, 6 and 7).

3) Quantitative analysis for stone clearance at specific time points per size of stone

Several trials assessed the stone clearance of different stone sizes at specific time points using either α-blocker (tamsulosin or urapidil) or nifedipine [13,15,18,23,24,25]. Stones included in the above studies were classified in two groups according to their size, stones ≤10 mm and > 10 mm. No significant difference in the stone clearance rate was detected between the different stone sizes (≤10 mm vs. > 10 mm) (p=0.81, p=0.07, p=0.44, respectively).

4) Quantitative analysis for stone clearance at specific time points per stone location

Pooling of trials with the use of α-blockers for the expulsion of stones located in the lower ureter or upper ureter and kidney showed no significant difference in the stone clearance rate between the different stone locations at 2 weeks [10-16] and 1 month (p=0.72 p=0.50, respectively) [14,19,21,24,25]. Similarly, pooling of trials including renal or upper ureteral stones showed no heterogeneity at approximately 2 [13,14,23,26] and 3 months (p = 0.58; I² = 0%; OR: 2.73; 95% CI: 1.69–4.40 and P = 0.98; I² = 0%; OR: 2.50; 95% CI: 1.69–3.71, respectively) [13,14,22,23,26,28,29,30]. No trials were found for lower ureteral stones at 2 and 3 months. As a result no comparison was applicable.

5) Quantitative analysis for medical expulsive therapy and time to stone expulsion.

5.1) α-Blockers

Pooling of 8 trials [17,20,22,23,24,25,26,30] demonstrated that the group receiving α-blockers had significantly decreased time to stone expulsion (WMD: -2.60; 95% CI: -4.80 to -0.40) in comparison to the control group (Figure 8).

5.2) Choreito

Pooling of 2 trials [28,34] demonstrated that choreito group had significantly decreased time to stone expul-
Systematic review and meta-analysis of the adjuvant role of Medical Expulsive Therapy (MET) in Shock Wave Lithotripsy (SWL) treatment of upper urinary stones, p. 32-44

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>MET</th>
<th>Control</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2.4.1 Tamsulosin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agorwal et al. 2009</td>
<td>19</td>
<td>20</td>
<td>2.0%</td>
<td>2.11 [0.18, 25.35]</td>
</tr>
<tr>
<td>Falahkar et al. 2011</td>
<td>50</td>
<td>70</td>
<td>27.5%</td>
<td>1.63 [0.81, 3.29]</td>
</tr>
<tr>
<td>Hussein et al. 2010</td>
<td>49</td>
<td>67</td>
<td>22.7%</td>
<td>2.22 [1.08, 4.56]</td>
</tr>
<tr>
<td>Naja et al. 2008</td>
<td>48</td>
<td>55</td>
<td>6.4%</td>
<td>2.91 [0.76, 11.19]</td>
</tr>
<tr>
<td>Singh et al., 2011a</td>
<td>54</td>
<td>59</td>
<td>9.8%</td>
<td>1.75 [0.33, 5.63]</td>
</tr>
<tr>
<td>Zaytoun et al., 2012 Tam</td>
<td>46</td>
<td>50</td>
<td>5.1%</td>
<td>2.19 [0.50, 9.61]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>317</td>
<td>308</td>
<td>73.4%</td>
<td>1.99 [1.32, 3.00]</td>
</tr>
<tr>
<td>Total events</td>
<td>266</td>
<td>225</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>65</td>
<td>65</td>
<td>13.4%</td>
<td>3.18 [1.33, 7.61]</td>
</tr>
<tr>
<td><strong>2.4.2 Alfuzosin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baloch et al. 2011</td>
<td>56</td>
<td>64</td>
<td>13.4%</td>
<td>3.18 [1.33, 7.61]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>56</td>
<td>43</td>
<td>13.4%</td>
<td>3.18 [1.33, 7.61]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>48</td>
<td>40</td>
<td>6.3%</td>
<td>1.71 [0.42, 7.04]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>102</td>
<td>78</td>
<td>13.2%</td>
<td>2.85 [1.17, 6.96]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>93</td>
<td>61</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>484</td>
<td>451</td>
<td>100.0%</td>
<td>2.26 [1.61, 3.19]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>415</td>
<td>329</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for subgroup differences</strong>: Chi² = 1.23, df = 2 (P = 0.26), I² = 0%</td>
<td></td>
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</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.78, df = 5 (P = 0.98); I² = 0%
Test for overall effect: Z = 3.27 (P = 0.001)

**Figure 7. Forest plot of comparison: α-blocker versus control; outcome: stone clearance at ~3 months per type of α-blocker. M-H, Mantel-Haenszel test; CI, Confidence interval; df, degree of freedom.**

6) Analgesic requirements

Only one study evaluated the need for analgesics and evaluated the effect of doxazosin. No significant difference in the need for analgesics was detected between doxazosin and placebo groups (OR=2.26, 95% CI: 0.76-6.67).

7) Dose of analgesics (mg)

Patients of the α-blocker group required significantly less dosage of analgesics as compared to the control group (STD=-1.15, 95% CI: -1.52 to -0.77).

8) Occurrence of pain

Patients receiving α-blockers (tamsulosin or doxazosin), experienced pain less frequently than the patients in the control group (OR=0.22, 95% CI: 0.12-0.38). One of the two trials with Rowatinex offered data regarding the occurrence of pain. No significant difference was observed between patients who received Rowatinex as compared to those who received placebo (OR: 3.27, 95% CI: 0.63-17.07).

9) Pain intensity (Visual Analog Scale).

The intensity of pain (as assessed by the VAS scores) in patients in the α-blocker group was lower than in the patients in the control group (STD=-0.57, 95% CI: -1.08 to 0.06). The intensity of pain was not significantly different between patients who received nifedipine and those who did not (WMD: + 3.20; 95% CI: -3.22 to +9.62). One trial with Rowatinex offered data regarding the VAS score. No significant difference was observed between the Rowatinex and the placebo group (WMD: 0.00, 95% CI: -0.27 to +0.27).

10) Steinstrasse.

Steinstrasse formation was significantly less frequent in the α-blocker group at 2 weeks (OR: 0.20, 95% CI: 0.05-0.80) and 3 months (OR:0.45, 95% CI: 0.25-0.81).
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[10,13,23,25,26,29,30]. No difference was detected at one month in the only study that offered relevant data (OR: 2.73, 95% CI: 0.50-15.03).

11) Auxiliary interventions

Requirement for auxiliary interventions was significantly decreased with MET pooling at 2 weeks [10,13] and at 3 months (OR: 0.29, 95% CI: 0.50-15.03, OR: 0.34, 95% CI: 0.50-15.03, respectively) [22,23,26].

12) Hospital visits

The use of α-blockers [10,11,25] suggested that the need for emergency visits to hospital was decreased in the α-blocker group as compared to the control group (OR: 0.34, 95% CI: 0.13-0.90). However, the mean number of emergency visits and hospital admissions was not significantly different. Only one study [11] evaluated mean number of emergency visits in patients treated with nifedipine. There was no significant difference between nifedipine and control groups (WMD: -0.04; 95% CI: -0.40 to +0.48).

Discussion

Results from this systematic review and meta-analysis demonstrate evidence for a higher overall pooled effect of α-blockers on stone expulsion rate at different time periods after SWL, suggesting a class effect for this type of MET. A favorable decrease in the time needed for successful stone fragments expulsion was also observed with α-blockers. The rationale of using α-blockers as MET is to decrease both the frequency and amplitude of ureteral peristalsis above the stone with reduction in ureteral spasm at the stone location [38]. These changes are accompanied by an increase in the intrarureteral urine flow and stone expulsion rate as the intrarureteral pressure decreases [39].

Pooled results demonstrated the efficacy of α-blockers in reducing the intensity of ureteral colic, as indicated by the lower VAS score and the reduced doses of analgesics needed. The potential of α-blockers in relieving ureteral colic and obstruction was proposed in literature and may be attributed to a decrease of ureteral peristaltic contractions rate accompanying the stone expulsion process [38]. In a meta-analysis, Hollingsworth et al. reported consistent benefit of tamsulosin in various pain parameters in patients with renal stones as well as ureterolithiasis with or without SWL [39].

The current evaluation demonstrated that overall pooled effect was in favor of nifedipine regarding the stone-free rate. A single study [11] showed that patients receiving nifedipine had a lower mean number of hospital visits. The intensity of pain was not significantly different between nifedipine and control group in one study [25]. Calcium-channel blocking agents and steroids have been used to reduce muscular tonus, decrease the inflammation, improve ureteral flow and reduce pain. Nevertheless, they are associated with bothersome side effects [40].

Rowatinex, a special terpene combination product, showed beneficial expulsive effect after SWL. Nevertheless, outcome measurements such as patients’ symptoms, renal colic and VAS score were not significantly different compared with the control group. Rowatinex is considered to have antilithogenic, antibacterial, anti-inflammatory, spasmylytic, and analgesic activities, which have been confirmed in preclinical experiments [42].

Two studies [20,34] showed the stone clearance was not significantly different at 1 month between the choreito
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and the control group. However, pooled results showed that the time to stone elimination was reduced in comparison to the control group. Choreito is usually used in Japan to treat acute cystitis. It prevents edema and inflammation and slightly increases urine volume. These effects would probably facilitate the early passage of stones [43]. Further studies are needed to evaluate the role of choreito.

Stone clearance appeared to be statistically increased in the Uriston group at the 1-month and 2-months time points. Studies have shown that Uriston, a Phyllanthus niruri extract after SWL for renal stones results in an increased stone-free rate that appears statistically significant for lower ureteral stones [35]. Nonetheless, solid conclusions can be drawn for the role of P. niruri.

The high likelihood of spontaneous passage for stones up to about 4 mm, may be considered to negatively influence the efficacy for MET due to the high spontaneous expulsion rate [3]. There was no statistically significant difference in expulsion rate between stones ≤ 10 mm and stones > 10 mm at 2 weeks, 1 month and 2 months after SWL when α-blockers were administered. Nevertheless, there was a trend towards a lower efficacy of MET for stones < 10 mm compared to stones > 10 mm at 1 month. The limited numbers of patients at 2 weeks and 2 months might be responsible for the undetectable significant differences in the treatment of smaller stones. Larger placebo controlled RCTs are warranted in order to confirm the correlation of stone clearance after SWL and the diameter of the stone.

Stone location did not seem to be a moderating factor on the efficacy of MET since our pooled data demonstrated that it is equal effective for renal/proximal ureteral compared to distal ureteral stones at 2 weeks and 1 month after SWL. Renal stone clearance is determined by the initial size and location of the stone, pelvi-caliceal configuration and dynamic urinary transport [44]. Regarding the clearance of ureteral stones, it is basically determined by ureteral peristalsis above the stone, spasm and edema at the location of stone [45]. It would be reasonable to assume that MET is effective for renal and proximal ureteral stones after SWL because the fragments have to pass the distal ureter. However, α-blockers are considered to be beneficial for proximal ureteral stone locations, as they mediate a 33% reduction in proximal ureteral tone [12]. Based on the findings of the included studies, the evidence is inconclusive as to whether the effectiveness of MET on stone clearance after SWL is correlated with stone location; a large confirmatory trial would elucidate the issue.

The reported rate of steinstrasse formation is generally 2–10% after SWL of renal stones depending on the initial stone size [46]. Steinstrasse after SWL has been classified according to the presence and size of the lead fragment; it has been reported to be relevant to the need for intervention [47]. Steinstrasse formation was significantly less frequent in the treatment group at 2 weeks and 3 months. However, this was not the case at 1 month, where no difference was detected in the only study that offered relevant data. Larger studies are required to evaluate the role of MET in the conservative management and pain management of steinstrasse after SWL.

The number of patients requiring auxiliary interventions after SWL was smaller in α-blockers group at 2 weeks and 3 months. The reduction in adjuvant procedures showed that MET could be a cost effective treatment for residual fragments after SWL.

Limitations

The vast majority of randomized studies incorporated into the present systematic review were predominantly small, single-institution, not blinded studies, with an inadequately or unclear allocation concealment leading to a trend towards overestimating the effectiveness of treatment effects. Moreover, despite...
the absence of statistical heterogeneity of our review, clinical heterogeneity can be expected, by including trials using different drugs with the same class effect, different doses or different formulations. Additional factors possibly increasing heterogeneity between studies were different follow-up periods defining treatment success or failure, different MET duration, differences in stone size and stone location determination using radiographs or computed tomography.

Conclusions

To our best knowledge, this study is the first report to assess the role of all types of MET in clearance of fragments after SWL of renal and ureteral stones. Evidence suggests that MET using α-blockers, nifedipine, Rowatinex and Uriston can be suggested as an adjuvant treatment after SWL owing to theirs expulsive efficacy, pain reduction, and safety profile. Although the level of evidence for MET is high, the lack of multicentre, randomized, placebo-controlled studies with larger numbers of patients possibly would result in an enhancement of the expulsive properties of the tested drugs. Further trials with a larger sample size and more carefully designed protocol are required to confirm these findings.

Conflicts of interest

The author declared no conflict of interest

References

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