PRISMA-combined $\alpha$-blockers and antimuscarinics for ureteral stent-related symptoms

A meta-analysis

Yu-ming Zhang, MD, Pei Chu, MD, Wen-jin Wang, MD

Abstract

Background: As a monotherapy, $\alpha$-blockers and anti-muscarinics are both efficacy for ureteral stent-related symptoms (SRS). The aim of the study was to systematically evaluate their efficacy of a combination therapy for SRS.

Methods: Relevant studies investigating $\alpha$-blockers and/or anti-muscarinics for SRS were identified through searching online databases including PubMed, EMBASE, Cochrane Library, and other sources up to March 2016. The RevMan software was used for data analysis, and sensitivity analysis and inverted funnel plot were also adopted.

Results: Seven randomized controlled trials (RCTs) and 1 prospective controlled trial including 545 patients were selected. Compared with $\alpha$-blockers, the combination group achieved significant improvements in total International Prostate Symptom Score (IPSS) [-3.93 (2.89, 4.96), $P<0.00001$, obstructive subscore [-1.29 (0.68, 1.89), $P<0.0001$, irritative subscore [-2.93 (2.18, 3.68), $P<0.00001$, and quality of life score [-0.99 (0.42, 1.55), $P<0.001$. Compared with antimuscarinics, there were also significant differences in total IPSS [-3.49 (2.43, 4.55), $P<0.00001$, obstructive subscore [-1.40 (0.78, 2.01), $P<0.0001$, irritative subscore [-2.10 (1.30, 2.90), $P<0.00001$, and quality of life score [-1.18 (0.58, 1.80), $P<0.001$ in favor of combination group. No significant difference was found in the visual analog pain score and the urinary symptoms score in Ureteral Stent Symptom Questionnaire (USSQ). No significant difference in complications was found.

Conclusions: Current analysis shows significant advantages of combination therapy compared with monotherapy of $\alpha$-blockers or antimuscarinics alone mainly based on IPSS. More RCTs adopting validated USSQ as outcome measures are warranted to support the finding.

Abbreviations: CI = confidence interval, IPSS = International Prostate Symptom Score, MD = mean difference, QoL = quality of life, RCTs = randomized controlled studies, RCTs = randomized controlled trials, RR = risk ratios, SD = standard deviation, SRS = stent-related symptoms, USSQ = Ureteral Stent Symptom Questionnaire, VAS = visual analog pain score.

Keywords: solifenacin, SRS, tamsulosin, terazosin, tolterodine, ureteric stent-related discomfort

1. Introduction

Ureteral stents are usually applied in urolithiasis, obstructive pyelonephritis, and after some endoscopic procedures in the case of ureteral edema and ureter perforation.[1,2] Though dilate urinary tract, they assist in kinds of aspects including ureter stone passage, renal pelvic pressure reduction, obstruction prevention, and injury recovery acceleration.[3] However, because of their invasion to all of renal, ureter, and bladder, discomforts and morbidities were also unavoidable to be related with stents insertion.

The reported morbidities mainly included lower urinary tract symptoms, pain, hematuria, and infections. A series of symptoms were demonstrated to be stent-related, and the stent-related symptoms (SRS) affected over 80% of the patients[4], and sometimes SRS also had obvious influence to general health status and work performance. To reduce the incidence of SRS, the material and size of stents were primary considered and adjusted. After that, some drugs that are effective in the treatment of benign prostatic hyperplasia-related symptoms are also attempted to be administrated in clinic.[5] Among kinds of drugs, $\alpha$-blockers and antimuscarinics were mostly adopted, and both of them were demonstrated to be helpful to relieve the severity of SRS in the patients[6,7].

Although comparative efficacy of the 2 drugs for SRS was still unclear due to different pharmacological effects between $\alpha$-blockers and antimuscarinics, some studies immediately supposed an advantage of combination therapy of both of them compared monotherapy of either of them.[8–15] Combined administration may finally enhance the therapeutic effects; however, results of previous studies with limited sample sizes were not completely consistent, and thus certain conclusions were absent. As ureteral stents were commonly used in urology even as a routine procedure after the ureter surgery, a more effective treatment method than before for SRS would be very practical for urologists. Therefore, we gathered all relevant prospective controlled studies to systematically evaluate the efficacy of combination therapy compared with monotherapy of $\alpha$-blockers and antimuscarinics for SRS.
2. Materials and methods

2.1. Search strategy

A comprehensive literature search was performed in PubMed, EMBASE, the Cochrane Library, and other sources such as clinical trial register centers up to 16 March 2016. Search terms were as followings: (alpha-blocker OR a-blocker OR tamsulosin) AND (antimuscarinic OR tolterodine OR solifenacin) AND (ureteral stent-related symptoms OR ureteric stent-related discomfort OR SRS). Detailed search strategy in PubMed can be found in Supplementary materials, http://links.lww.com/MD/B557. At the same time, references and related articles of potential clinical studies and reviews were also manually checked. Language was limited to English.

2.2. Inclusion criteria

Published studies investigated the efficacy of combination therapy of α-blockers and antimuscarinics versus monotherapy of α-blockers or antimuscarinics were considered. Study designs were limited to prospective clinical controlled trials, whereas reviews, case series, retrospective studies, and animal studies were excluded. Participants were patients undergoing a double-J ureter stent placement after urinary surgery, due to ureteral stones and/or other diseases. Interventions were α-blockers, antimuscarinics, and anesthetics on demand. Patients in the control group (monotherapy group) received either α-blockers or antimuscarinics, whereas patients in the treatment group (combination group) received both of them. Specific drugs administrated in the included trials were tamsulosin, terazosin, tolterodine, and solifenacin.

Outcome measures used to present the efficacy and safety of the therapy as follows. Primary outcomes included International Prostate Symptom Score (IPSS). Secondary outcomes included Ureteral Stent Symptom Questionnaire (USSQ), quality of life (QoL) score, visual analog pain score (VAS), and complications.

2.3. Data abstraction

According to the inclusion criteria, searched citations were primarily screened by the titles and abstracts to exclude nonrelevant studies. And potential citations for inclusion were further confirmed by full-texts evaluation. After that, the basic characteristics, methodological quality items, and data of outcome measures were abstracted in predefined tables. The process was completed by 2 reviewers and cross-checked independently.

2.4. Quality assessment

The quality of included studies was assessed by using the methods recommended by the Cochrane Handbook, which included 6 domains: randomization, allocation concealment, blinding of participant and outcome measurement, incomplete outcomes, selective reporting, and other bias. It reflected the risk of bias possibly located in the process of selection, performance, detection, follow-up, reporting, and others.

2.5. Statistical analysis

The RevMan software (5.3 version, recommended by the Cochrane Collaboration) was used to analyze the data of outcomes. The clinical heterogeneity was first handled by subgroup analyzes, and then statistical heterogeneity was tested by the Q statistic and the chi-2 statistic, which was presented as the value of I2. Significant heterogeneity was considered when I2 > 50%, and a random-effects was used. Otherwise, a fixed-effect model was used. Mean difference (MD) with 95% confidence interval (CI) was used to reflect the overall effect size for continuous variances, and risk ratio (RR) with 95%CI was used for dichotomous variances. For continuous outcomes, changes from the level of baseline (mean1+SD1) to the level of outcome measured time (mean2+SD2) were first calculated using the formula as previously reported in the treatment group and in the control group, respectively: \( r = \frac{\text{mean}_2 - \text{mean}_1}{\text{SD}_1} \). For continuous outcomes, changes from the level of baseline (mean1+SD1) to the level of outcome measured time (mean2+SD2) were first calculated using the formula as previously reported in the treatment group and in the control group, respectively: \( \text{MD} = \frac{\text{mean}_2 - \text{mean}_1}{\text{SD}_1} \). For continuous outcomes, changes from the level of baseline (mean1+SD1) to the level of outcome measured time (mean2+SD2) were first calculated using the formula as previously reported in the treatment group and in the control group, respectively: \( \text{MD} = \frac{\text{mean}_2 - \text{mean}_1}{\text{SD}_1} \).

3. Results

3.1. Characteristics of the included studies

Literature search yielded 167 citations, and a total of 8 trials containing 269 cases in the monotherapy group and 276 cases in the combination group were finally included (Fig. 1). Among the included studies, 7 of them were designed as randomized controlled trials (RCTs) and 1 was prospective controlled trial. Baseline characteristics were presented in Table 1. As shown, the sex ratio and average age were comparable. Mainly primary disease was ureteral stones, and only 1 trial also included a small proportion of transitional cell carcinoma patients. The stent size was reported to be fixed in 4 trials, and to be adjusted by weight and height in 2 trials, and the other 2 trials did not report detailed information. Average duration of stent insertion ranged from 8.7 days to 23.3 days across the trials.
and 2 studies had unclear risk in randomization, and only 1 included tolterodine in 5 trials and solifenacin in 3 trials. Methodology was low to moderate. One study had high risk of allocation concealment and 4 studies had low risk in blinding (Table 2).

3.2. International prostate symptom score (IPSS)

Meta-analysis results of 4 studies involving 182 patients, and administrated antimuscarinics included tolterodine in 5 trials and solifenacin in 3 trials.

Quality assessment results showed that the overall quality of methodology was low to moderate. One study had high risk and 2 studies had unclear risk in randomization, and only 1 study had low risk in allocation concealment and 4 studies had low risk in blinding (Table 2).

Compared with antimuscarinics alone, combination therapy also achieved a significant reduction in the total IPSS score by a mean of 3.49 (95% CI, 2.43–4.53, P < 0.00001), the obstructive subscore by a mean of 1.40 (95% CI, 0.78–2.01, P < 0.00001), and the irritative subscore by a mean of 2.10 (95% CI, 1.30–2.90, P < 0.00001), as shown in Figs. 2 and 3.

3.3. Urinary symptoms score

Meta-analysis results of urinary symptoms score in USSQ involving 182 patients, and also significantly reduced the score by a mean of 1.18 (95% CI, 0.58–1.80, P = 0.0002) compared with antimuscarinics alone, as shown in Fig. 4.

3.5. Visual analog pain score (VAS)

Meta-analysis results of 4 studies involving 182 patients, and showed that there was no significant difference between the combination group and the monotherapy group of either a-blocker (MD = 0.45, 95% CI [-0.15, 0.45], P = 0.90) or antimuscarinic (MD = 0.63, 95% CI [-0.35, 1.62], P = 0.21), as shown in Fig. 5.

### Table 1

Baseline characteristic of included trials.

| Study            | Case (M/C) | Sex (M/F) | Age (M/C) | Dose of drugs            | Size | Stent | Primary disease               |
|------------------|------------|-----------|-----------|--------------------------|------|-------|------------------------------|
| Lee 2010         | 15/20      | 10/5      | 14/6      | 43.3 ± 11.3/46.4 ± 13.0  | 9.6 Fr ± 6.4/11.4 ± 5.5 | Urine stones                  |
| Lim 2011         | 43/32      | 24/19     | 22/10     | 49.9 ± 15.2/50.7 ± 11.5  | 6 Fr | 14/14 | Urine stones                  |
| Tehrnich 2013    | 23/24      | 16/7      | 19/5      | 36.2 ± 11.3/23.4 ± 8.9   | 4.8 Fr | 16/16 | Urine stones                  |
| Shalaby 2013     | 82/84      | 55/27     | 58/26     | 41 ± 17/44 ± 18           | Adjusted | NR | NR                           |
| Shelbaia 2014    | 20/20      | NR        | NR        | 33.4 ± 9.9                | NR | NR | Urine stones                  |
| Streeper 2014    | 30/34      | NR        | NR        | 51.8                      | NR | 9.9 ± 10.6 | Urine stones            |
| Park 2015        | 20/18      | 9/11      | 11/7      | 54.5 ± 13.4/54.8 ± 11.3   | 6 Fr | 22.9 ± 1.7 | Urine stones              |
| Salingam 2016    | 36/44      | 21/15     | 19/25     | 51.5/51.3                | Adjusted | 8.7 ± 10.6 | Urine stones and others    |

Data was presented as mean ± standard deviation or mean value.

M = monotherapy group, C = combination group, M = male, F = female, NR = not reported.

3.4. Quality of life (QoL)

Meta-analysis results of 6 studies including 609 cases reported QoL. Combination therapy significantly reduced the QoL score by a mean of 0.99 (95% CI, 0.42–1.55, P = 0.0007) compared with α-blockers alone, and also significantly reduced the score by a mean of 1.18 (95% CI, 0.58–1.80, P = 0.0002) compared with antimuscarinics alone, as shown in Fig. 4.

### Table 2

Quality assessment of included studies.

| Study            | Randomization | Allocation concealment | Blinding | Incomplete data | Selective reporting | Other bias |
|------------------|---------------|------------------------|----------|-----------------|---------------------|------------|
| Lee 2010         | UR, mentioned | UR                     | UR       | LR              | LR                  | LR         |
| Lim 2011         | HR, controlled study | HR                | HR, open-label | LR              | LR                  | LR         |
| Tehrnich 2013    | LR, random table | LR                 | LR, double blind | LR              | LR                  | LR         |
| Shalaby 2013     | LR, random sequence | LR         | LR        | LR              | LR                  | LR         |
| Shelbaia 2014    | UR, mentioned | UR                     | UR       | LR              | LR                  | LR         |
| Streeper 2014    | LR, random sequence | UR              | LR, double blind | LR              | LR                  | LR         |
| Park 2015        | LR, random sequence | UR            | LR, open-label | LR              | LR                  | LR         |
| Salingam 2016    | LR, random sequence | LR         | LR        | LR              | LR                  | LR         |

HR = high risk, LR = low risk, UR = unclear risk.
3.6. Complications

Only 2 studies \[8,14\] reported the data of treatment-related complications, and the others stated that no related complication was found. Meta-analysis results demonstrated no significant difference between combination and monotherapy (RR = 0.84, 95%CI [0.25, 2.82], \(P = 0.78\)). The reported complications were mild, which included fatigue, dyspepsia, dizziness, constipation, vision blurred, and abdominal discomfort.

3.7. Sensitivity analysis

For outcomes measures combined in the fixed-effect model, though converting the combined model into the random-effect model, the changing trends were not altered in aspects of total IPSS, the obstructive subscore, the irritative subscore, and complications between combination therapy with \(\alpha\)-blockers or antimuscarinics alone. For outcomes measures combined in the random-effect model, though omitting study with high risks\[9\],
the changing trends were not altered in aspects of QoL and VAS between combination therapy with antimuscarinics, while altered in outcomes of VAS between combination therapy with α-blockers (MD= 0.70, 95%CI [−0.26, 1.65], P= 0.15).

3.8. Publication bias
Inverted funnel plots indicated that risks of bias might exist in outcomes of obstructive subscore and VAS. However, low risks of bias may exist in outcomes of total IPSS score, irritative subscore, and QoL score (Supplementary materials, http://links.lww.com/MD/B557).

4. Discussion
The use of α-blockers and antimuscarinics for SRS was mainly based on the similarity of lower urinary tract symptoms frequently happened in benign prostatic hyperplasia and overactive bladder. α-Blockers was also adopted as first-line drugs in medical explosive therapy for ureteral stones, and it was reported to be able to maintain the baseline frequency of spontaneous contractility while reduce the persisted pressure in ureter. For antimuscarinics, they can inhibit the activity of muscarinic receptor and the involuntary contraction of bladder. As a stent affected both ureter and bladder, combined α-blocker and anti-muscarinic may be a very promising therapy for SRS.

Our meta-analysis included 8 studies and showed significant benefits of combination therapy than α-blockers or antimuscarinics alone for SRS. The results showed that the combination group was associated with significantly reduced total IPSS score, obstructive subscore, and irritative subscore. IPSS was actually a specific questionnaire for benign prostatic hyperplasia. It
The limitations of current study were as follows. (1) In methodological quality assessment, only 1 study properly performed allocation concealment, and 4 studies adopted blinding. Allocation concealment as an action to prevent the grouping information from being known by the investigators who had the sequence number, it can be realized by sealed envelopes or center-controlled system. And blinding of participants and outcomes assessment would avoid subjective bias from participants and investigators, and can be achieved by placebo and other methods. The risks existed in these items might to some extent overestimate the effect size. Future RCTs should pay more attentions in the study design to increase the reliability. (2) For outcomes, current analysis results mainly based on IPSS is similar but more comprehensive and reliable than a previous meta-analysis. As mentioned above USSQ is superior to IPSS for patients suffered SRS, although 3 of the included studies adopted USSQ as outcome measure, limited to insufficient sample size and data presentation, only a descriptive analysis was conducted and the primary results focusing on other items besides urinary symptoms were really attracting. (3) All of the material, size, position, and duration of inserted stent have some influence to outcomes, although they were comparable in each study, they might cause unavoidable heterogeneity across the studies. (4) Publication bias always existed and was largely unrecognized, which had been well addressed in previous studies. After applying the methods of inverted funnel plots, high risk of publication bias may exist in outcomes of obstructive subscore andVAS, which might also have negative influence to the reliability of the results.

5. Conclusions

Current analysis shows significant advantages of combination therapy compared with monotherapy of either α-blockers or antimuscarinics mostly based on outcome measures in IPSS. More well-designed RCTs adopting validated USSQ as primary outcome measures are warranted to supporting the finding.

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