Comparison of Alpha-Blockers and Antimuscarinics in Improving Ureteral Stent-Related Symptoms: A Meta-Analysis

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Purpose: A meta-analysiswas conducted to compare alpha-blocker (AB) and antimuscarinic (AM) monotherapies in releasing US-related symptoms.

Methods: A comprehensive literature search was performed on online databases PubMed, Web of Science, Medline, and Cochrane library. Ureteric Symptom Score Questionnaire (USSQ), International Prostate Symptom Score (IPSS), quality of life (QoL) and visual analogue pain scale (VAPS) were pooled and compared.

Results: Nine full-text articles met the inclusion criteria and have been included. The studies were conducted in 9 different centers between 2009 and 2016. All articles were RCT studies and a total of 654 patients were recorded totally, among which 323 were given alpha-blockers while others were given antimuscarinics. Although patients using alpha-blockers presented lower USSQ scores, no statistically significant difference was recorded in urinary symptom(SMD 0.5, 95 % CI -0.2 to 1.20, $P = 0.159$), pain(SMD 0.33, 95 % CI -0.26 to 0.92, $P = 0.280$),general health, work performance(SMD-0.34, 95 % CI -0.08 to 0.76, $P = 0.115$) and sexual performance (all $p > 0.05$) (SMD 0.12, 95 % CI -0.10 to 0.34, $P = 0.280$). Meanwhile IPSS (SMD -0.10, 95 % CI -0.32 to 0.11, $P = 0.358$), QoL(SMD-0.03, 95 % CI -0.23 to 0.18, $P = 0.802$) and VAPS(SMD 0.08, 95 % CI -0.15 to 0.31, $P = 0.447$) were similar between the two groups (all $P > 0.05$).

Conclusion: The analysis suggests that AB showed a similar effect with AM. It is necessary to conduct a larger and more detailed cohort study and find the population that potentially might benefit most by AM.

Keywords: alpha-Blockers; antimuscarinics; ureteral stent-related symptoms; meta-analysis

INTRODUCTION

Indwelling ureteral stent (US) is common during endourological practice since 1967[1]. However,it has been reported that 38% to 80% patients ever experienced stent related symptoms[2,3], which may be caused by the spasm of ureteric smooth musculature around the indwelling foreign object. Alpha-blockers (AB) efficacy is already proven in releasing stent-related morbidity[4, 5]. The potential mechanism may include the reduction of bladder irritation symptoms due to involuntary bladder contraction. Meanwhile, antimuscarinics (AM) have been used to overcome symptoms caused by the involuntary overactive contraction of the bladder due to the distal end of the stent in the urinary bladder, with encouraging results[6].A randomized clinical trial has proved that preoperative administration of oral tolterodine could reduce catheter related bladder discomfort after percutaneous nephrolithotomy[7].

Several cohort studies and meta-analysis have demonstrated the superiority of either AB or AM to placebo on alleviating US-related symptoms[8,9,10]. However, there are still limited studies to compare the therapeutic effect on US-related symptom between AB and AM. To address this issue, we gathered the available prospective randomized controlled studies and conducted a meta-analysisto investigate if a statistically significant difference exist between AB and AM monotherapies in releasing US-related symptoms.

METHODS

Literature search and selection

A systematic and comprehensive literature search of on-

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Received September 2017 & Accepted April 2018

Table 1. Characteristics of the included studies in the meta-analysis.

Year	Design	Treatment	Outcomes	Duration	Total N	α-blocker N	Antimuscarinic N	Stent size	Jadad score
2016	RCT	Tamsulosin 0.4mg QD Oxybutynin 5mg QD	USSQ,QoL	day 7	34	17	17	24/26cm;6F	3
2016	RCT	Tamsulosin 0.4mg QD Solifenacin 5mg QD	USSQ	day 14	87	44	43	24/26cm;6F	3
2016	RCT	Tamsulosin 0.4mg QD Solifenacin 5mg QD	USSQ	day 21	117	59	58	24/26/28cm;4.7/6/7F	5
2015	RCT	Tamsulosin 0.2mg QD Solifenacin 5mg QD	USSQ	day 14	40	20	20	20/22/24/26/28cm;6F	3
2013	RCT	Terazosin 2mg Bid Tolterodine 2mg QD	IPSS,VAPS,QoL	NG	46	23	23	28cm;4.8F	5
2013	RCT	Tamsulosin 0.4mg QD Solifenacin 10mg QD	IPSS,VAPS,QoL	day 14	160	80	80	NG	5
2012	RCT	Doksazosin 4 mgQD Tolterodine 4 mg QD	IPSS,QoL	NG	42	21	21	26/28cm;4.7F	5
2011	RCT	Tamsulosin 0.2mg QD Solifenacin 5mg QD	IPSS,VAPS,QoL	day 14	88	43	45	24/26cm;6F	3
2009	RCT	Alfuzosin 10mg QD Tolterodine 4mg QD	USSQ	day 42	40	20	20	24-28cm;6F	5

line databases PubMed (National Library of Medicine, Bethesda, MD, US), Web of Science (Thompson Scientific, Philadelphia, PA, US), Embase, and Cochrane library was performed to identify randomized controlled trials(RCTs) before February 28th,2017. Search strategy was as following:(alpha-blocker OR α-blocker OR tamsulosin) AND (antimuscarinic OR tolterodine OR solifenacin) AND (ureteral stent-related symptoms OR ureteric stent-related discomfort OR SRS).Meanwhile,references and related articles of clinical studies and reviews were also manually checked. Language was limited to English. The therapeutic effects of AB and AM on patients with US-related symptoms were examined.

We evaluated all search results according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement[11]. The selection of original studies was based on the process of viewing titles, abstracts and full papers. The inclusion criteria were as following:(1) studies focused on patients with US insertion;(2) comparative studies examining effect of AB versus AM;(3) RCTs studies;(4) comparative studies that reported at least one outcome of interest. Non-comparative studies, review articles, abstracts, case reports, editorials, expert opinions, commentary articles, and letters were excluded.

Data extraction and quality assessment

Data were extracted independently by two investigators (Y.Y. Gao and H.R. Liang) and conflicts were adjudicated by a third investigator (W.Q. Wu). Information about all available variables from selected studies was extracted. Ureteric Symptom Score Questionnaire (USSQ)[12]including urinary symptom, pain, general health, work performance and sexual performance, International Prostate Symptom Score (IPSS), quality of life (QoL)[13] and visual analogue pain scale (VAPS) were used to evaluate the outcomes. Quality assessment was assessed using the JADAD scoring[14].

Statistical analysis

Standardized mean difference (SMD) with 95% CI was calculated for outcomes. Cochran's X2 test and I2 were used to examine the heterogeneity among effect estimates. Statistical heterogeneity among studies was defined as I2 statistic greater than 50%. Fixed effects model was preferred to random effects model when there was no statistically significant heterogeneity and vice versa when there was significant heterogeneity[15]. Study bias was detected using the methods of Funnel plots and the egger and Begger's test[16]. Statistical significance was taken as two-sided $P < 0.05$. The analysis was conducted with STATA 12.0 (Stata Corporation College Station, TX, USA)

RESULTS

Study selection and quality assessment

Initially 146 records were screened and 38 additional relevant studies were identified after a hand searching inspection. 153 papers remained after excluding duplicates. After an in-depth review, 9 full-text articles met the inclusion criteria and were considered in the analysis[6,17-24] (**Figure 1**).

All of the articles were RCT studies with a total of 654 patients. 323 patients were treated with AB monotherapy while 331 were treated with AM monotherapy. All studies gained 6 or 7 score in study quality assessment (**Table 1**).

Ureteric Symptom Score Questionnaire (USSQ)

USSQ was presented for evaluating the US-related symptoms including frequency, urgency, pain, dysuria,

Table2. SummarySWD of Ureteric Symptom Score Questionnaire of Alpha-blockers versus antimuscarinic.

Outcomes	Study number	Heterogeneity I2(%)	Statistical Method	Summary SWD(%)(95%CI)
Urinary symptom	5	88.2	random	0.50 [-0.2,1.20], $P = 0.159$
Pain	5	83.9	random	0.33 [-0.26,0.92], $P = 0.280$
General health	5	68.9	random	0.34 [-0.08,0.76], $P = 0.115$
Work performance	5	54.9	random	0.29 [-0.05,0.64], $P = 0.098$
Sexual performance	5	20.8	random	0.12 [-0.10,0.34], $P = 0.280$

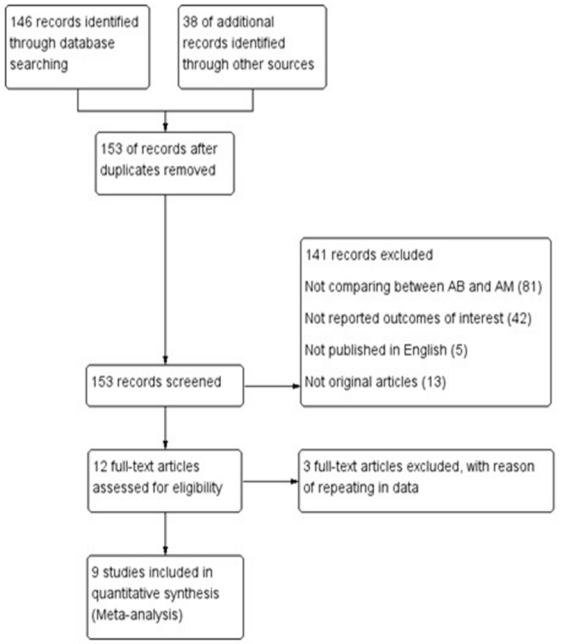

Figure 1. flow diagram detailing the search strategy and identification of studies used in Meta-analysis

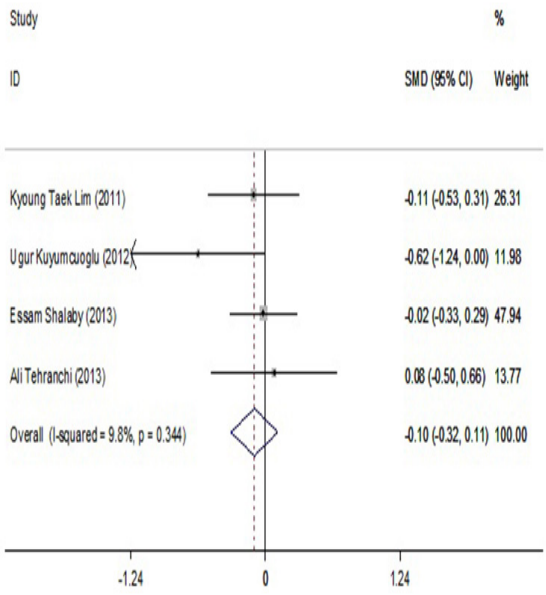

Figure 2. . Forest plot of International prostate symptom score (IPSS) of Alpha-blockers versus antimuscarinic

incomplete emptying and hematuria. Random effects model was used in the five groups. Although lower USSQ score was noticed in patients using AB compared with AM group in all items, urinary symptom (SMD 0.5, 95 % CI -0.2 to 1.20, $P = 0.159$), pain (SMD 0.33, 95 % CI -0.26 to 0.92, $P = 0.280$), general health (SMD-0.34, 95 % CI -0.08 to 0.76, $P = 0.115$), work performance (SMD 0.29, 95 % CI -0.05 to 0.64, $P = 0.098$) and sexual performance (SMD 0.12, 95 % CI -0.10 to 0.34, $P = 0.280$) there is no significant difference (**Table 2**).

International prostate symptom score (IPSS)

The IPSS was lower in patients treated with AB monotherapy than in patients treated with AM monotherapy in fixed model, but no significantly (SMD -0.10, 95 % CI -0.32 to 0.11, $P = 0.358$), with low heterogeneity (I2 = 9.8%, $p = 0.344$) (**Figure 2**).

Quality of life (QoL)

6 studies including 370 cases reported QoL. Fixed model was used. No significant difference was found between AB and AM monotherapies (SMD-0.03, 95 % CI -0.23 to 0.18, $P = 0.802$), with no heterogeneity (I2 = 0, $p = 0.425$) (**Figure 3**).

Visual Analog Pain Score (VAPS)

The present meta-analysis in fixed model indicated that the VAPS was similar between AB or AM (SMD 0.08, 95 % CI -0.15 to 0.31, $P = 0.447$), with low heterogeneity (I2 = 21.8, $p = 0.279$) (**Figure 4**).

Publication bias and sensitivity analysis

Visual inspection of funnel plots suggested there was no obviously asymmetric distribution of main outcomes. Begger and Egger's test confirmed there was no significant publication bias (**Table 3**). A sensitivity analysis was performed by excluding the studies with the lowest-quality score. This did not influence the results.

DISCUSSION

To our knowledge, this is the first meta-analysis aimed to evaluate the efficacy of AB and AM monotherapies in relieving US-related symptoms. We did not observed statistically significant superiority of AB in overcoming stent-related symptoms compared to AM. The analysis suggests that both drugs can effectively treat US-related symptoms.

Despite a growing number of studies on US-related symptoms, explicit pathophysiology is still matter of debate. Lang et al.[25] proposed that US-related pain and urinary symptoms may be the result of ureteric spasm or trigonal irritation. Pain and lower urinary tract symptoms (LUTS) caused by stent could be worsened by the increasing pressure transmitted to the renal pelvis during urination, bladder ischemia and lower ureteric and bladder spasm[26,27]. A US may also exacerbate pre-ex-

Table 3. Assessment for publication bias.

Outcomes	Number of estimates	*P* value for Begg's test	*P* value for Egger's test
General health	5	0.806	0.908
Urinary symptom	5	0.462	0.572
Pain score	5	0.806	0.907
Work performance	5	1	0.927
Sexual performance	5	0.462	0.457
IPSS	4	0.308	0.592
QoL	5	0.806	0.588
VAPS	3	0.296	0.297

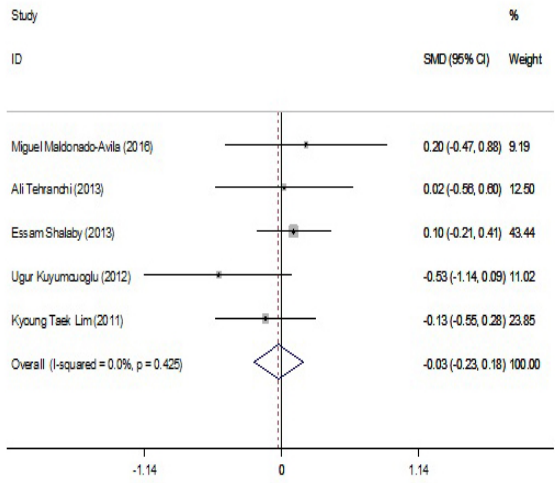

Figure 3. Forest plot of Quality of life (QoL) of Alpha-blockers versus antimuscarinic

isting subclinical detrusor over-activity and induce overactive bladder symptoms[28].

AB are the first-line treatment for LUTS, while AM are widely used for the treatment of overactive bladder. Both drugs have been applied to treat US-related symptoms in clinical practice. AB could reduce the US-induced pain during voiding probably determining a relaxation of bladder neck/prostatic smooth musculature and consequently reducing voiding pressure and urinary reflux[29]. Flank pain may be the result of ureter spasm in patients with indwelling US, AB may relieve it by decreasing ureteral spasm and vescico-ureteral reflux[30].

Ureteral Stent Symptom Questionnaire(USSQ), International Prostate Symptom Score (IPPS), Visual Analogue Pain Score (VAPS) and Quality of Life (QoL) are measuring tools used in the included studies about ureteral stent-related symptoms. USSQ was designed to characterize urinary symptoms associated with stent

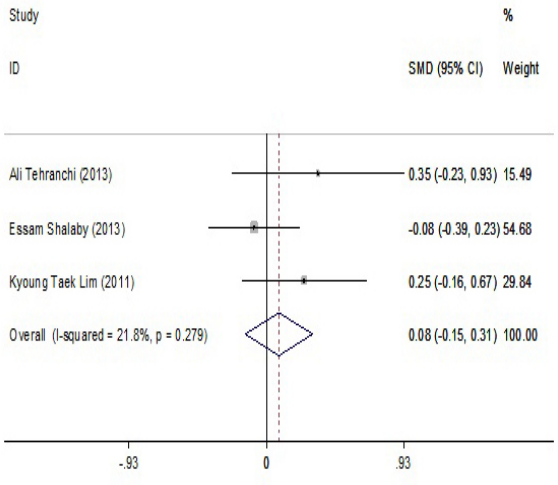

Figure 4. Forest plot of Visual Analog Pain Score (VAPS) of Alpha-blockers versus antimuscarinic

including frequency, urgency, pain, dysuria, incomplete emptying and hematuria. IPSS was used as frequently as USSQ for assessing stent-related symptoms, which was divided into the total score, obstructive symptom score, and irritative symptom score. Analogue Pain Scale graded from 1 (minimal or no symptoms) to 10 (symptoms of maximal severity).

In endourological clinical practice, AB are much more commonly used than AM to release US-related symptoms. However, our results suggest that AM were not significantly inferior in improving US-related symptoms if compared to AB. Thus, AM can be a valid alternative to AB in this category of patients.

This study has some limitations. First, many clinical factors and any underlying ureteral disease would have influenced the outcomes, and different patient characteristics also may have a negative influence on the overall results. Second, different types of intra-corporeal lithotripsy and dose difference of medications to patients were not sub-analyzed in our study because of data limitation. Third, since majority of included studies reported an insufficient follow-up period, consequently, we were unable to evaluate the outcomes varying from time.

CONCLUSIONS

In conclusion, the analysis suggests that AB showed a similar effect with AM. Although lower USSQ and IPSS score were noticed in patients using AB compared with AM group in all items, but without statistically significant difference, and equally no significant difference were found between AB and AM monotherapies in the way of QoL and VAPS. It is necessary to conduct a larger and more detailed cohort study and find the population that potentially might benefit most by AM.

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