ORIGINAL RESEARCH

Efficacy of α-blocker in improving ureteral stent-related symptoms: a meta-analysis of both direct and indirect comparison

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Objective: To critically evaluate the efficacy of an α-blocker in improving ureteral-stent-related symptoms and preliminarily investigate the difference between different types of α-blockers.

Methods: Relevant randomized controlled trials were identified through searching PubMed, the Cochrane Library, Embase, and other sources. After quality assessment and data abstraction, direct comparison based on the Ureteral Stent-related Symptom Questionnaire (USSQ) between α-blockers and control was performed by RevMan 5.3. Indirect comparison between different types of α-blockers was performed by ITC 1.0. Sensitive and subgroup analyses were used to handle important clinical factors.

Results: Sixteen randomized controlled trials containing 1,489 cases were included. Compared with control, α-blockers significantly reduced the overall urinary symptom, pain index, general health index, and scores related to sexual matters, while no significant difference was found in work performance and additional problem scores. Subgroup analysis showed that the duration of stent insertion, patient's age, stent size, and the type of α-blocker had the potential to influence the outcomes. Through indirect comparison, we found alfuzosin and terazosin to be better than tamsulosin in pain relief and general health improvement.

Conclusion: α-Blocker was effective in treating ureteral stent-related symptoms, as it improved the major indexes of USSQ post-insertion or post-removal. Alfuzosin and terazosin seemed to be better than tamsulosin, which needs further verification because of the lack of direct comparison currently.

Keywords: α-blocker, tamsulosin, alfuzosin, terazosin, ureteral stent-related discomfort

Introduction

The ureteral stent (US) was first reported in 1967 by Zimskind et al.[1] Although concerted efforts to clarify its necessity were made and reduced frequency of stent placement was desired, it is still widely used in urological clinical practice to some extent as routine intervention after surgery.[2] As a foreign body inserted in the ureter, part of renal pelvis, and bladder, US covers a relatively wide proportion of the urinary system and, of course, induces a series of discomforts called US-related symptoms (USSs).[3] It was reported that more than half of the patients would suffer from the incidence of frequency, urgency, dysuria, and incomplete emptying,[4,5] and these together with pain and other discomforts would further negatively impact the general health status, sexual activity, and work performance in ~78% of cases.[6] And after a US insertion, the quality of life was reported to be affected in 45%–80% of the patients.[7]

To minimize the severity of USSs, much effort has been made. Although the material, size, length, and position of the stent were fully considered and gradually

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improved, the management after stent insertion was still a longstanding challenge for both the patient and the surgeon. To prevent and treat USSs, some investigators administrated drugs including selective endogenous α-antagonists and antimuscarinics, which are mostly used to treat urinary symptoms of benign prostatic hyperplasia.[8,9] Among them, α-1 blockers were reported to be one of the most promising drugs in patients with USSs because of their pharmacological effects of ureteral smooth relaxation and trigone inhibition.[10] And, in order to investigate the efficacy of α-1 blockers, a series of randomized controlled trials (RCTs) were conducted in the past decade.[11–26] However, since they were limited to small sample sizes and patient characteristics, the therapeutic effects were varied and thus different conclusions were drawn. Therefore, in this study we comprehensively gathered all the available RCTs together to clarify the overall and individual efficacy of α-1 blockers, and preliminarily investigated some factors important to the clinician.

Methods
Data sources and search strategies
The databases PubMed, Embase, and the Cochrane Library were comprehensively searched to identify RCTs comparing α-blocker and placebo control in preventing and treating USSs. The literature search was performed by adopting free terms and subject headings. The free terms included "alpha-blocker", "α-blocker", "alpha blocker", "tamsulosin", "terazosin", "doxazosin", "alfuzosin", "naftopidil", "silodosin", "ureteral stent-related symptoms", and "USS". Other sources and strategies to widen the search results included 1) screening the references and citations of the relevant RCTs, meta-analysis, and reviews; 2) manually searching the websites of clinical register centers and professional journals on urology; and 3) the use of some other search engine such as Google Scholar.

Inclusion criteria and study selection
The study type should be an RCT that used a random method to divide participants into different groups. And as reported, the participants should be patients who had a US (also known as double-J ureteral stent) through laparoscopic or open procedures for various underlying diseases. According to the result of randomization, additional α-blockers including tamsulosin, alfuzosin, terazosin, and doxazosin were administrated in the treatment group (α-blocker group), while placebo (or not), routine antibiotics for ~5 days, and analgesic on demand were administrated in the control group. The study mainly adopted the index of Ureteral Stent-related

Symptom Questionnaire (USSQ) as outcome measure. The USSQ is a specific USS scoring system and has six sections. Primary outcome measures were urinary symptoms, pain index (based on a visual analog scale from 1 to 10 at four locations in women and five locations in men), and general health; and secondary outcomes were work performance, sexual matters, and additional problems; other indexes were quality of life score, pain, irritative symptoms score, and obstructive symptoms score. Only relevant RCTs published in English language up to November 2015 were included. Reviews, case reports, and non-RCTs were excluded.

We screened the search results strictly following the inclusion and exclusion criteria. After assessing the titles and abstracts, final selection of an articles was made based on full-text evaluation.

Data abstraction and quality assessment
Data were entered in a predesigned table and the statistical software by two authors independently. The following items were abstracted: article information (first author, publication year, and case), participant baseline characters (age, sex, intervention, duration of stent, stent size, and outcome measured time), and outcome measures. Methodological quality was assessed by the following fields: randomization, allocation concealment, blinding (participant and outcome assessment blinding), incomplete outcome data, selective reporting of result, and any other bias.[27] The results of data abstraction and quality assessment were cross-checked to eliminate the possibility of human error.

Statistical analysis
The overall effect of α-blocker compared to control was initially analyzed by conditional meta-analysis using RevMan 5.3 (the Cochrane collaboration, Copenhagen, Denmark). According to the clinical importance, subgroup analyis of outcome measured time (post-insertion 1–2 weeks, 3–4 weeks, and post-removal) was first conducted. Data were calculated as mean difference (MD), standard MD (SMD), or risk ratio (RR), together with their 95% confidence interval (95% CI). Only random-effects model was adopted, as it would provide a more conservative estimate. A difference with $P<0.05$ was considered statistically significant. In order to investigate the influence of other clinical factors, we carried out sensitivity analysis according to the variables as follows: study quality (excluding poor-quality trials), age (separating patients >50 years and ≤50 years), size of stent (separating diameter <6F and ≥6F), and the type of α-blockers (separating tamsulosin and other α-blockers).

To preliminarily investigate the difference of α-blockers where direct comparison study was currently lacking, we made an indirect comparison of network analysis between tamsulosin and other α-blockers using ITC 1.0 (Canadian Agency for Drugs and Technologies in Health, Ontario, Canada) due to the limited number of available RCTs.

Results

Study characteristics

The primary search yielded 296 citations. After screening the titles and abstracts, full texts of 24 citations were evaluated, and finally a total of 16 RCTs were included (Figure 1). The meta-analysis contained 1,489 cases, of whom 772 patients were in the α-blocker group and 717 patients were in the control group. The baseline characteristics are presented in Table 1. The included studies covered four types of α-1 blockers: tamsulosin in ten trials,[12,14–17,21,23–26] alfuzosin in four trials,[11,13,20,24] terazosin in two trials,[18,22] and doksazosin in one trial.[19] The above drugs used in most trials were within the recommended dose of 0.4 mg/d, 10 mg/d, 2 mg/d, and 4 mg/d, and the duration of drug administration was in accordance with the duration of the stent, which ranged from 1 week to 6 weeks. The stent size was fixed in each trial, which ranged from 4.7F to 7F across trials. The length was reported in the trials to be fixed,[15,17,22] or adjusted by the height and weight of the patients. The outcome measured time ranged from 3 days to 1 week, 2 weeks, and 4 weeks post-insertion of the stent, and 2–4 weeks post-removal of stent.

Methodological quality assessment showed that the overall quality was moderate (Figure 2), as four trials might have potential bias and they did not report the details of randomization and blinding.[12,16,17,19]

Urinary symptom score

Compared with control, α-blockers significantly decreased the mean urinary symptom score (I^2=94%, MD =−3.47, 95% CI, −4.58, −2.36, P<0.00001). Subgroup analysis according to outcome measured time showed that α-blockers
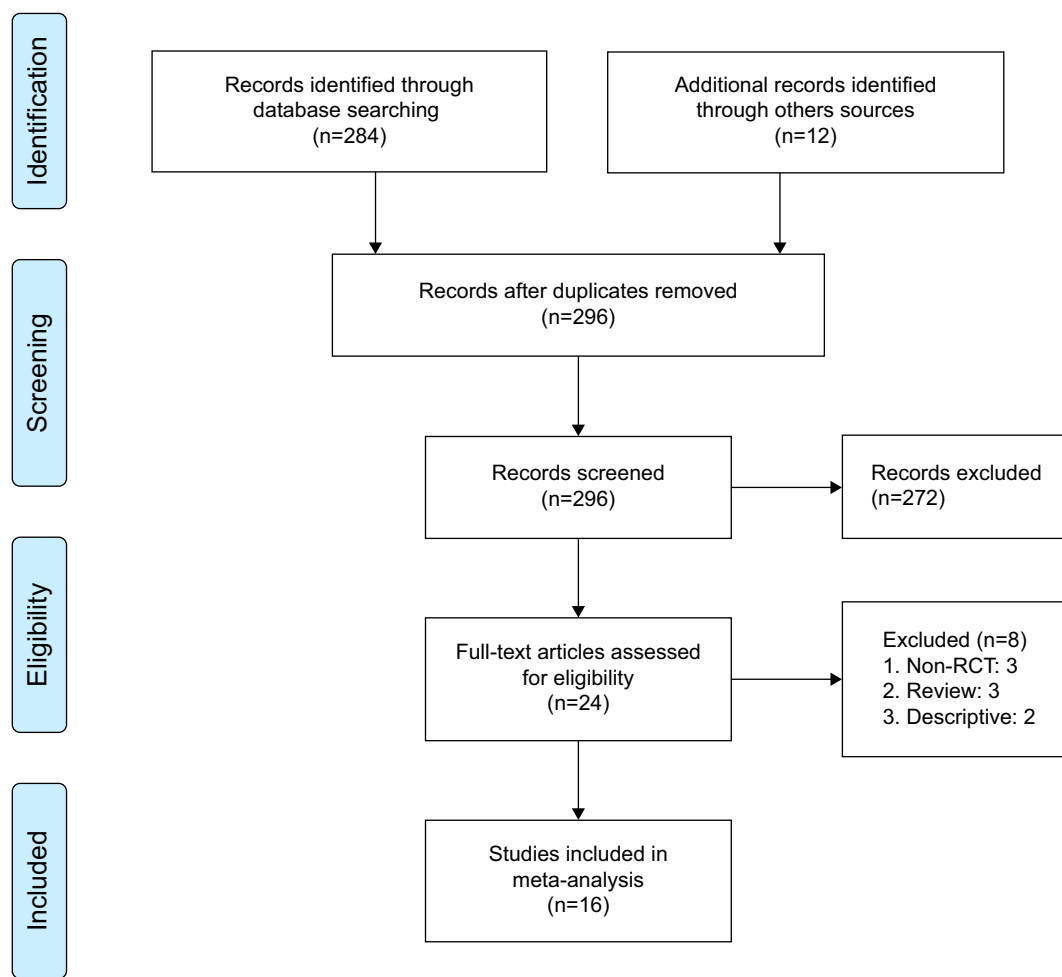

Figure 1 PRISMA flow diagram.
Abbreviations: RCT, randomized controlled trial; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1 Baseline characteristics of included RCTs

Study	Year	Case (T/C, n)	Age (T/C, y)	Sex (male/female)		Intervention (T/C)	Duration	Stent (size/length, cm)	Outcome measured time
				T	C				
Deliveliotis et al[11]	2006	50/50	53.1/55.3	30/20	27/23	10 mg alfuzosin for 4 weeks/placebo	4 weeks	5F/26–28	PI 4 weeks
Damiano et al[12]	2008	38/37	–	29/46		0.4 mg tamsulosin for 4 weeks/control	2 weeks	7F/–	PI and PR 1 week
Beddingfield et al[13]	2009	26/29	45.8/44.0	7/19	16/13	10 mg alfuzosin for 8 days/placebo	8.3/11.5 days	–	PI 3 days
Wang et al[14]	2009	79/75	50.1/51.5	63/16	58/17	0.4 mg tamsulosin for 2 weeks/placebo	2 weeks	7F/–	PI 1 week, and PR 2 weeks
Wang et al[15]	2009	75/71	50.4/50.8	61/14	55/16	0.4 mg tamsulosin for 2 weeks/placebo	2 weeks	7F/26	PI 2 weeks
Navanimitkul and Lojanapiwat[16]	2010	21/21	46.1/51.5	9/12	6/15	0.4 mg tamsulosin for 4 weeks/control	4 weeks	6F/–	PI 2 weeks and 4 weeks
Shelbaia and Elnashar[17]	2011	69/67	35.0/29.0	44/25	50/17	0.4 mg tamsulosin for 4 weeks/control	4 weeks	6F/26	–
Mokhtari et al[18]	2011	33/33	–	–	–	2 mg terazosin for 4 weeks/control	4 weeks	4.8F/–	PI 4 weeks
Kuyumcuoglu et al[19]	2012	21/21	45.2/42.9	15/6	7/14	4 mg doksazosin for 4 weeks/control	–	4.7F/26–28	PI 4 weeks
Nazim and Ather[20]	2012	65/65	37.8/40.1	52/13	49/16	10 mg alfuzosin for 1 week/placebo	>1 week	4.7–6F/–	PI 1 week
Shalaby et al[21]	2013	82/81	41.3/44	55/27	50/31	0.4 mg tamsulosin for 2 weeks/control	–	–	PI 2 weeks
Tehranchi et al[22]	2013	23/24	38.4/33.4	16/7	21/3	2 mg terazosin for 13.5 days/placebo	13.5/15.4 days	4.8F/28	PI 2 weeks
Singh et al[23]	2014	30/30	32.7/31.4	14/16	20/10	0.4 mg tamsulosin for 4 weeks/placebo	6 weeks	4–5F/24–26	PI 4 weeks
Dellis et al[24]	2014	50/50	45.6/46.9	25/25	26/24	0.4 mg tamsulosin for 4 weeks/placebo	4 weeks	6F/24–26	PI 1 and 4 weeks, and PR 4 weeks
Dellis et al[24]	2014	50/50	47.3/46.9	23/27	26/24	10 mg alfuzosin for 4 weeks/placebo			
Park et al[25]	2015	20/23	54.5/48.7	9/11	14/9	0.2 mg tamsulosin for 2 weeks/control	2 weeks	6F/20–28	PI 2 weeks, and PR 4 weeks
El-Nahas et al[26]	2015	40/40	41.4/40.8	19/21	24/16	0.4 mg tamsulosin for 5 weeks/placebo	5.1/4.8 weeks	6F/24–26	PI 1–2 weeks

Notes: Prulifloxacin 600 mg once daily for 5 days;[12] ciprofloxacin 500 mg twice daily for 5 days;[17] patients in α-blocker groups were administered an additional week of antibiotic therapy;[19] ciprofloxacin 500 mg twice daily for 5 days;[23] and 1 week of oral antibiotics (one tablet quinolone two times).[25]
Abbreviations: RCT, randomized controlled trial; T, treatment group; C, control group; y, years; PI, post-insertion of stent; PR, post-removal of stent.

significantly improved the urinary symptom score during post-insertion 1–2 weeks by a mean of −3.54 (95% CI, −6.54 to −0.55),[13,14,24–26] during 3–4 weeks[11,23,24] by a mean of −4.40 (95% CI, −5.16 to −3.64), and post-removal by a mean of −2.0 (95% CI, −2.55 to −1.46),[14,24,25] as shown in Figure 3.

Pain index score

Compared with control, α-blockers significantly decreased the mean pain index score (I^2=98%, MD =−0.89, 95% CI, −1.15, −0.63, $P<0.00001$). Subgroup analysis according to outcome measured time showed that α-blockers significantly reduced pain during post-insertion 1–2 weeks by a mean of −1.58 (95% CI, −3.04 to −0.12),[13,14,16,21,22,25,26]

during 3–4 weeks by a mean of −0.79 (95% CI, −1.24 to −0.34),[11,16–18,23] and post-removal by a mean of −0.03 (95% CI, −1.16 to 1.11),[14,25] as shown in Figure 4.

General health index score

Compared with control, α-blockers significantly decreased the mean general health index score (I^2=96%, MD =−0.50, 95% CI, −0.66, −0.34, $P<0.00001$). Subgroup analysis according to outcome measured time showed that α-blockers significantly improved general health index score during post-insertion 1–2 weeks by a mean of −0.62 (95% CI, −1.45 to 0.21),[13,14,16,24–26] during 3–4 weeks by a mean of −0.62 (95% CI, −0.92 to −0.33),[11,16,17,23,24] and post-removal by a

Figure 2 Methodological assessment.

mean of −0.50 (95% CI, −0.77 to −0.23),[14,24,25] as shown in Figure 5.

Sensitivity analysis and network meta-analysis

Sensitivity analysis showed that, after omitting trials with poor quality, the heterogeneity decreased. The results seemed to show that α-blockers had a weak influence on the urinary symptom score and general health index for patients >50 years and on pain index for stent ≥6F. By separating tamsulosin and other α-blockers, we found other α-blockers seemed to have more comprehensive effects.

And, indirect comparison between tamsulosin and other α-blockers through network meta-analysis indicated that the other α-blockers might have a superiority in pain index score and general health score (Table 2).

Work performance score

Compared with control, α-blockers did not induce any significant difference (I^2=93%, MD =1.07, 95% CI, −0.15, 2.30, P=0.09). Subgroup analysis according to outcome measured time showed that there was no significant difference between them during post-insertion 1–2 weeks,[13,14,25,26] 3–4 weeks,[23] and post-removal.[14,25]
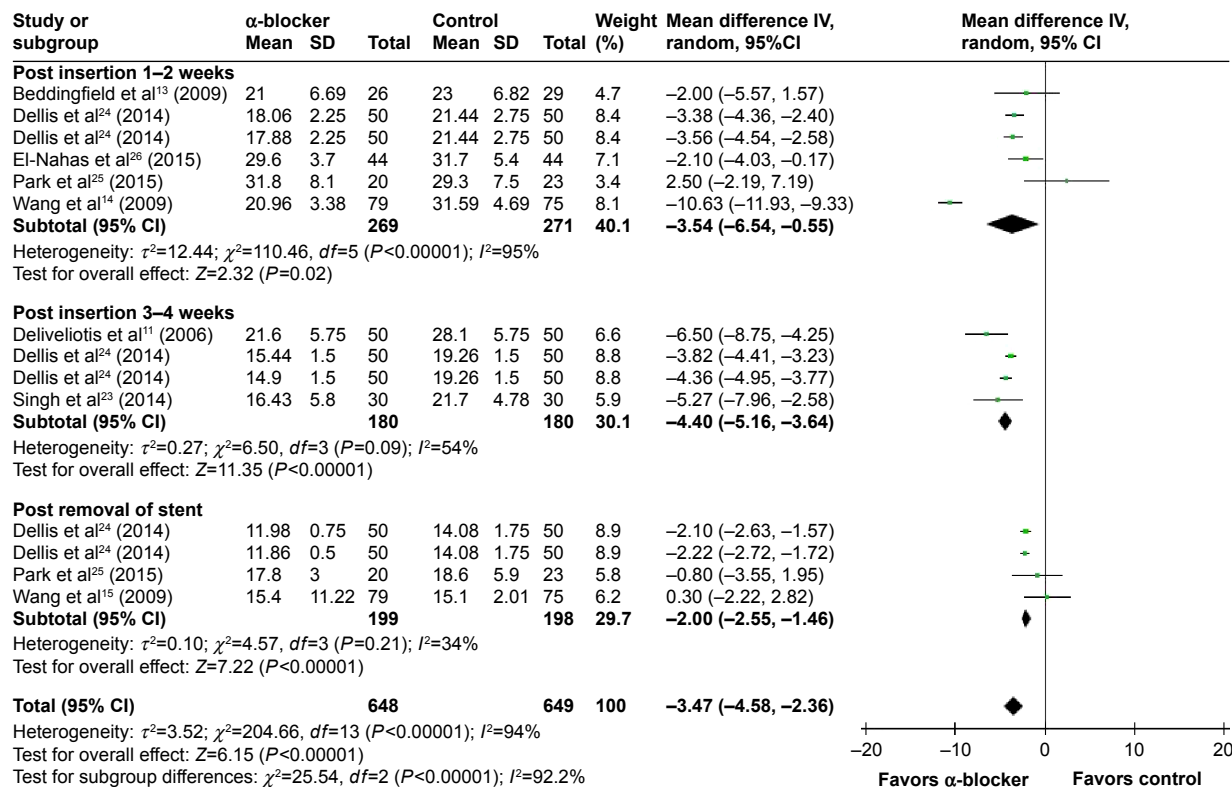
Study or subgroup	α-blocker			Control			Weight (%)	Mean difference IV, random, 95%CI	Mean difference IV, random, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Post insertion 1–2 weeks									
Beddingfield et al[13] (2009)	21	6.69	26	23	6.82	29	4.7	−2.00 (−5.57, 1.57)	
Dellis et al[24] (2014)	18.06	2.25	50	21.44	2.75	50	8.4	−3.38 (−4.36, −2.40)	
Dellis et al[24] (2014)	17.88	2.25	50	21.44	2.75	50	8.4	−3.56 (−4.54, −2.58)	
El-Nahas et al[26] (2015)	29.6	3.7	44	31.7	5.4	44	7.1	−2.10 (−4.03, −0.17)	
Park et al[25] (2015)	31.8	8.1	20	29.3	7.5	23	3.4	2.50 (−2.19, 7.19)	
Wang et al[14] (2009)	20.96	3.38	79	31.59	4.69	75	8.1	−10.63 (−11.93, −9.33)	
Subtotal (95% CI)			269			271	40.1	−3.54 (−6.54, −0.55)	

Heterogeneity: $\tau^2=12.44$; $\chi^2=110.46$, $df=5$ ($P<0.00001$); $I^2=95\%$
Test for overall effect: $Z=2.32$ ($P=0.02$)

Post insertion 3–4 weeks									
Deliveliotis et al[11] (2006)	21.6	5.75	50	28.1	5.75	50	6.6	−6.50 (−8.75, −4.25)	
Dellis et al[24] (2014)	15.44	1.5	50	19.26	1.5	50	8.8	−3.82 (−4.41, −3.23)	
Dellis et al[24] (2014)	14.9	1.5	50	19.26	1.5	50	8.8	−4.36 (−4.95, −3.77)	
Singh et al[23] (2014)	16.43	5.8	30	21.7	4.78	30	5.9	−5.27 (−7.96, −2.58)	
Subtotal (95% CI)			180			180	30.1	−4.40 (−5.16, −3.64)	

Heterogeneity: $\tau^2=0.27$; $\chi^2=6.50$, $df=3$ ($P=0.09$); $I^2=54\%$
Test for overall effect: $Z=11.35$ ($P<0.00001$)

Post removal of stent									
Dellis et al[24] (2014)	11.98	0.75	50	14.08	1.75	50	8.9	−2.10 (−2.63, −1.57)	
Dellis et al[24] (2014)	11.86	0.5	50	14.08	1.75	50	8.9	−2.22 (−2.72, −1.72)	
Park et al[25] (2015)	17.8	3	20	18.6	5.9	23	5.8	−0.80 (−3.55, 1.95)	
Wang et al[15] (2009)	15.4	11.22	79	15.1	2.01	75	6.2	0.30 (−2.22, 2.82)	
Subtotal (95% CI)			199			198	29.7	−2.00 (−2.55, −1.46)	

Heterogeneity: $\tau^2=0.10$; $\chi^2=4.57$, $df=3$ ($P=0.21$); $I^2=34\%$
Test for overall effect: $Z=7.22$ ($P<0.00001$)

Total (95% CI)			648			649	100	−3.47 (−4.58, −2.36)	

Heterogeneity: $\tau^2=3.52$; $\chi^2=204.66$, $df=13$ ($P<0.00001$); $I^2=94\%$
Test for overall effect: $Z=6.15$ ($P<0.00001$)
Test for subgroup differences: $\chi^2=25.54$, $df=2$ ($P<0.00001$); $I^2=92.2\%$

Favors α-blocker   Favors control

Figure 3 Meta-analysis results of mean urinary symptom score.
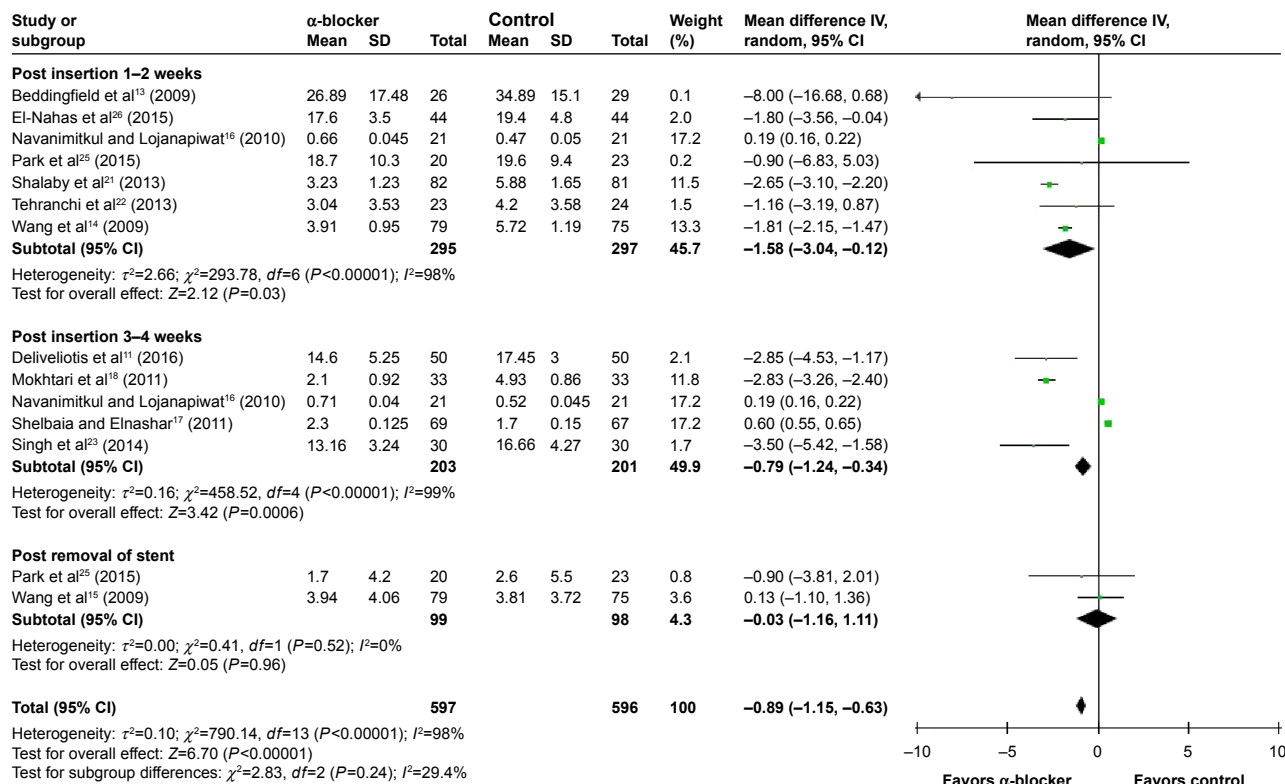**Abbreviations:** 95% CI, 95% confidence interval; df, degrees of freedom.

Study or subgroup	α-blocker			Control			Weight (%)	Mean difference IV, random, 95% CI	Mean difference IV, random, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Post insertion 1–2 weeks									
Beddingfield et al[13] (2009)	26.89	17.48	26	34.89	15.1	29	0.1	−8.00 (−16.68, 0.68)	
El-Nahas et al[26] (2015)	17.6	3.5	44	19.4	4.8	44	2.0	−1.80 (−3.56, −0.04)	
Navanimitkul and Lojanapiwat[16] (2010)	0.66	0.045	21	0.47	0.05	21	17.2	0.19 (0.16, 0.22)	
Park et al[25] (2015)	18.7	10.3	20	19.6	9.4	23	0.2	−0.90 (−6.83, 5.03)	
Shalaby et al[21] (2013)	3.23	1.23	82	5.88	1.65	81	11.5	−2.65 (−3.10, −2.20)	
Tehranchi et al[22] (2013)	3.04	3.53	23	4.2	3.58	24	1.5	−1.16 (−3.19, 0.87)	
Wang et al[14] (2009)	3.91	0.95	79	5.72	1.19	75	13.3	−1.81 (−2.15, −1.47)	
Subtotal (95% CI)			295			297	45.7	−1.58 (−3.04, −0.12)	

Heterogeneity: $\tau^2=2.66$; $\chi^2=293.78$, $df=6$ ($P<0.00001$); $I^2=98\%$
Test for overall effect: $Z=2.12$ ($P=0.03$)

Post insertion 3–4 weeks									
Deliveliotis et al[11] (2016)	14.6	5.25	50	17.45	3	50	2.1	−2.85 (−4.53, −1.17)	
Mokhtari et al[18] (2011)	2.1	0.92	33	4.93	0.86	33	11.8	−2.83 (−3.26, −2.40)	
Navanimitkul and Lojanapiwat[16] (2010)	0.71	0.04	21	0.52	0.045	21	17.2	0.19 (0.16, 0.22)	
Shelbaia and Elnashar[17] (2011)	2.3	0.125	69	1.7	0.15	67	17.2	0.60 (0.55, 0.65)	
Singh et al[23] (2014)	13.16	3.24	30	16.66	4.27	30	1.7	−3.50 (−5.42, −1.58)	
Subtotal (95% CI)			203			201	49.9	−0.79 (−1.24, −0.34)	

Heterogeneity: $\tau^2=0.16$; $\chi^2=458.52$, $df=4$ ($P<0.00001$); $I^2=99\%$
Test for overall effect: $Z=3.42$ ($P=0.0006$)

Post removal of stent									
Park et al[25] (2015)	1.7	4.2	20	2.6	5.5	23	0.8	−0.90 (−3.81, 2.01)	
Wang et al[15] (2009)	3.94	4.06	79	3.81	3.72	75	3.6	0.13 (−1.10, 1.36)	
Subtotal (95% CI)			99			98	4.3	−0.03 (−1.16, 1.11)	

Heterogeneity: $\tau^2=0.00$; $\chi^2=0.41$, $df=1$ ($P=0.52$); $I^2=0\%$
Test for overall effect: $Z=0.05$ ($P=0.96$)

Total (95% CI)			597			596	100	−0.89 (−1.15, −0.63)	

Heterogeneity: $\tau^2=0.10$; $\chi^2=790.14$, $df=13$ ($P<0.00001$); $I^2=98\%$
Test for overall effect: $Z=6.70$ ($P<0.00001$)
Test for subgroup differences: $\chi^2=2.83$, $df=2$ ($P=0.24$); $I^2=29.4\%$

Favors α-blocker   Favors control

Figure 4 Meta-analysis results of mean pain index score.
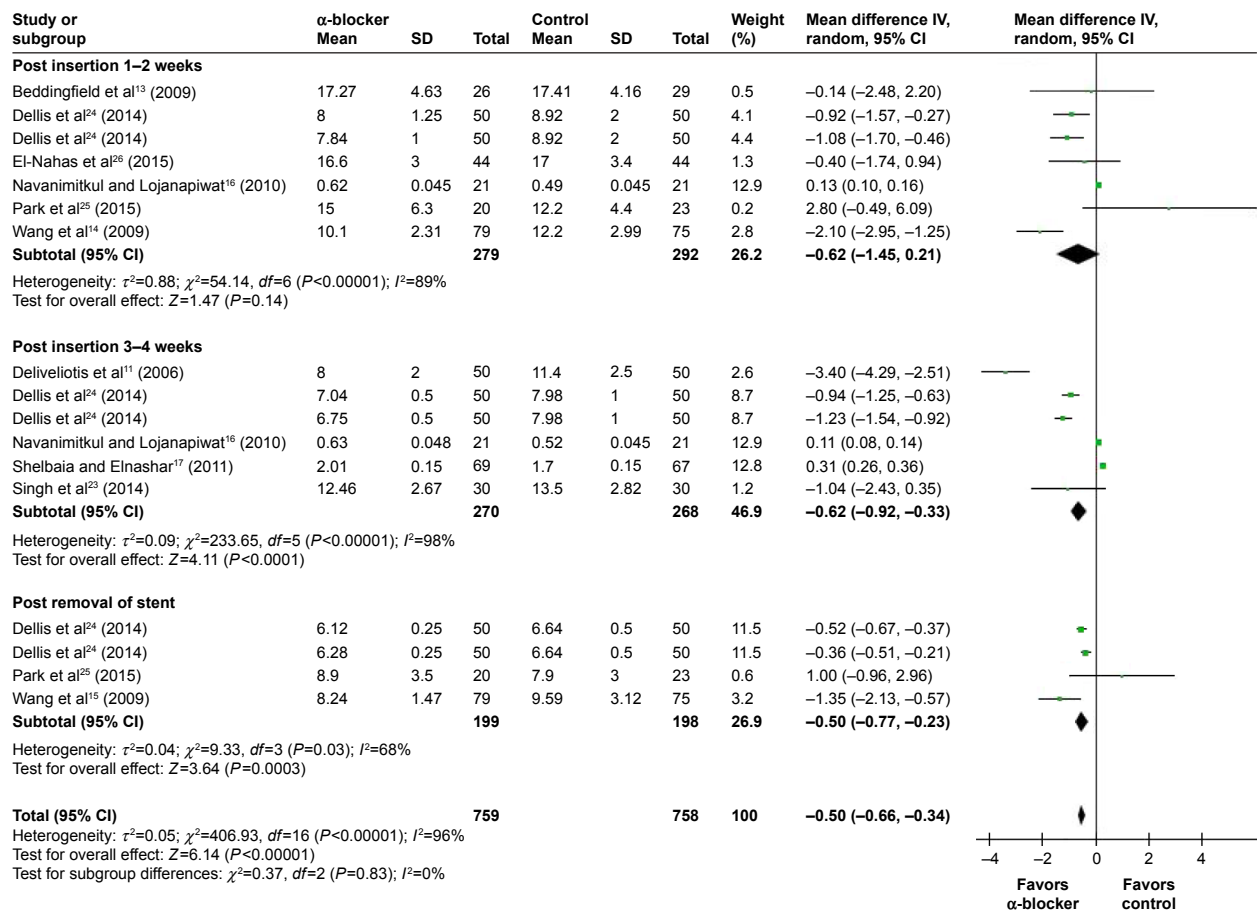**Abbreviations:** 95% CI, 95% confidence interval; df, degrees of freedom.

Study or subgroup	α-blocker Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI	Mean difference IV, random, 95% CI
Post insertion 1–2 weeks									
Beddingfield et al[13] (2009)	17.27	4.63	26	17.41	4.16	29	0.5	–0.14 (–2.48, 2.20)	
Dellis et al[24] (2014)	8	1.25	50	8.92	2	50	4.1	–0.92 (–1.57, –0.27)	
Dellis et al[24] (2014)	7.84	1	50	8.92	2	50	4.4	–1.08 (–1.70, –0.46)	
El-Nahas et al[26] (2015)	16.6	3	44	17	3.4	44	1.3	–0.40 (–1.74, 0.94)	
Navanimitkul and Lojanapiwat[16] (2010)	0.62	0.045	21	0.49	0.045	21	12.9	0.13 (0.10, 0.16)	
Park et al[25] (2015)	15	6.3	20	12.2	4.4	23	0.2	2.80 (–0.49, 6.09)	
Wang et al[14] (2009)	10.1	2.31	79	12.2	2.99	75	2.8	–2.10 (–2.95, –1.25)	
Subtotal (95% CI)			279			292	26.2	–0.62 (–1.45, 0.21)	

Heterogeneity: $\tau^2=0.88$; $\chi^2=54.14$, $df=6$ ($P<0.00001$); $I^2=89\%$
Test for overall effect: $Z=1.47$ ($P=0.14$)

Post insertion 3–4 weeks									
Deliveliotis et al[11] (2006)	8	2	50	11.4	2.5	50	2.6	–3.40 (–4.29, –2.51)	
Dellis et al[24] (2014)	7.04	0.5	50	7.98	1	50	8.7	–0.94 (–1.25, –0.63)	
Dellis et al[24] (2014)	6.75	0.5	50	7.98	1	50	8.7	–1.23 (–1.54, –0.92)	
Navanimitkul and Lojanapiwat[16] (2010)	0.63	0.048	21	0.52	0.045	21	12.9	0.11 (0.08, 0.14)	
Shelbaia and Elnashar[17] (2011)	2.01	0.15	69	1.7	0.15	67	12.8	0.31 (0.26, 0.36)	
Singh et al[23] (2014)	12.46	2.67	30	13.5	2.82	30	1.2	–1.04 (–2.43, 0.35)	
Subtotal (95% CI)			270			268	46.9	–0.62 (–0.92, –0.33)	

Heterogeneity: $\tau^2=0.09$; $\chi^2=233.65$, $df=5$ ($P<0.00001$); $I^2=98\%$
Test for overall effect: $Z=4.11$ ($P<0.0001$)

Post removal of stent									
Dellis et al[24] (2014)	6.12	0.25	50	6.64	0.5	50	11.5	–0.52 (–0.67, –0.37)	
Dellis et al[24] (2014)	6.28	0.25	50	6.64	0.5	50	11.5	–0.36 (–0.51, –0.21)	
Park et al[25] (2015)	8.9	3.5	20	7.9	3	23	0.6	1.00 (–0.96, 2.96)	
Wang et al[15] (2009)	8.24	1.47	79	9.59	3.12	75	3.2	–1.35 (–2.13, –0.57)	
Subtotal (95% CI)			199			198	26.9	–0.50 (–0.77, –0.23)	

Heterogeneity: $\tau^2=0.04$; $\chi^2=9.33$, $df=3$ ($P=0.03$); $I^2=68\%$
Test for overall effect: $Z=3.64$ ($P=0.0003$)

Total (95% CI)			759			758	100	–0.50 (–0.66, –0.34)	

Heterogeneity: $\tau^2=0.05$; $\chi^2=406.93$, $df=16$ ($P<0.00001$); $I^2=96\%$
Test for overall effect: $Z=6.14$ ($P<0.00001$)
Test for subgroup differences: $\chi^2=0.37$, $df=2$ ($P=0.83$); $I^2=0\%$

Figure 5 Meta-analysis results of mean general health index score.
Abbreviations: 95% CI, 95% confidence interval; *df*, degrees of freedom.

Sexual matters score

Compared with control, α-blockers significantly decreased the mean sexual matters score ($I^2=71\%$, MD =–0.29, 95% CI, –0.44, –0.15, $P<0.0001$). Subgroup analysis according to outcome measured time showed that α-blockers significantly improved sexual matters during post-insertion 1–2 weeks by a mean of –0.42 (95% CI, –0.91 to 0.06),[13,14,24–26] 3–4 weeks by a mean of –0.44 (95% CI, –0.64 to –0.24),[11,24] and post-removal by a mean of –0.21 (95% CI, –0.35 to –0.06),[14,24,25] as shown in Figure 6.

Table 2 Sensitivity analysis and indirect-comparison meta-analysis results

	Urinary symptom score		Pain index score		General health index score		Sexual matters score	
	I^2	MD (95% CI)	I^2	MD (95% CI)	I^2	MD (95% CI)	I^2	MD (95% CI)
Sensitivity analysis								
High-quality study	52%	–3.87 (–4.47, –3.28)	0%	–2.71 (–3.00, –2.42)	76%	–1.25 (–1.73, –0.77)	75%	–0.36 (–0.64, –0.09)
Age ≤50 y	36%	–3.77 (–4.27, –3.27)	0%	–2.69 (–3.06, –2.32)	0%	–1.05 (–1.24, –0.86)	79%	–0.35 (–0.72, 0.01)*
>50 y	94%	–5.35 (–11.01, 0.31)*	0%	–1.85 (–2.18, –1.51)	86%	–1.67 (–3.62, 0.28)*	0%	–0.55 (–0.75, –0.34)
Stent <6F	54%	–4.92 (–7.29, –2.54)	0%	–2.74 (–3.03, –2.44)	83%	–1.70 (–3.75, 0.34)*	0%	–0.59 (–0.82, –0.37)
≥6F	95%	–4.15 (–5.79, –2.50)	99%	–0.08 (–0.31, 0.15)*	96%	–0.29 (–0.45, –0.14)	75%	–0.33 (–0.65, –0.02)
Tamsulosin	95%	–4.32 (–6.83, –1.82)	99%	–0.52 (–0.78, –0.27)	95%	–0.14 (–0.29, 0.01)*	81%	–0.41 (–0.91, 0.09)*
Other α-blockers#	58%	–3.94 (–4.98, –2.90)	20%	–2.66 (–3.35, –1.97)	89%	–1.48 (–2.62, –0.34)	18%	–0.47 (–0.66, –0.29)
Indirect comparison								
Tamsulosin vs other α-blockers		–0.38 (–3.09, 2.33)*		2.14 (1.41, 2.88)		1.34 (0.19, 2.49)		0.06 (–0.39, 0.51)*

Notes: *No significant difference was found. #Other α-blockers included alfuzosin and terazosin.
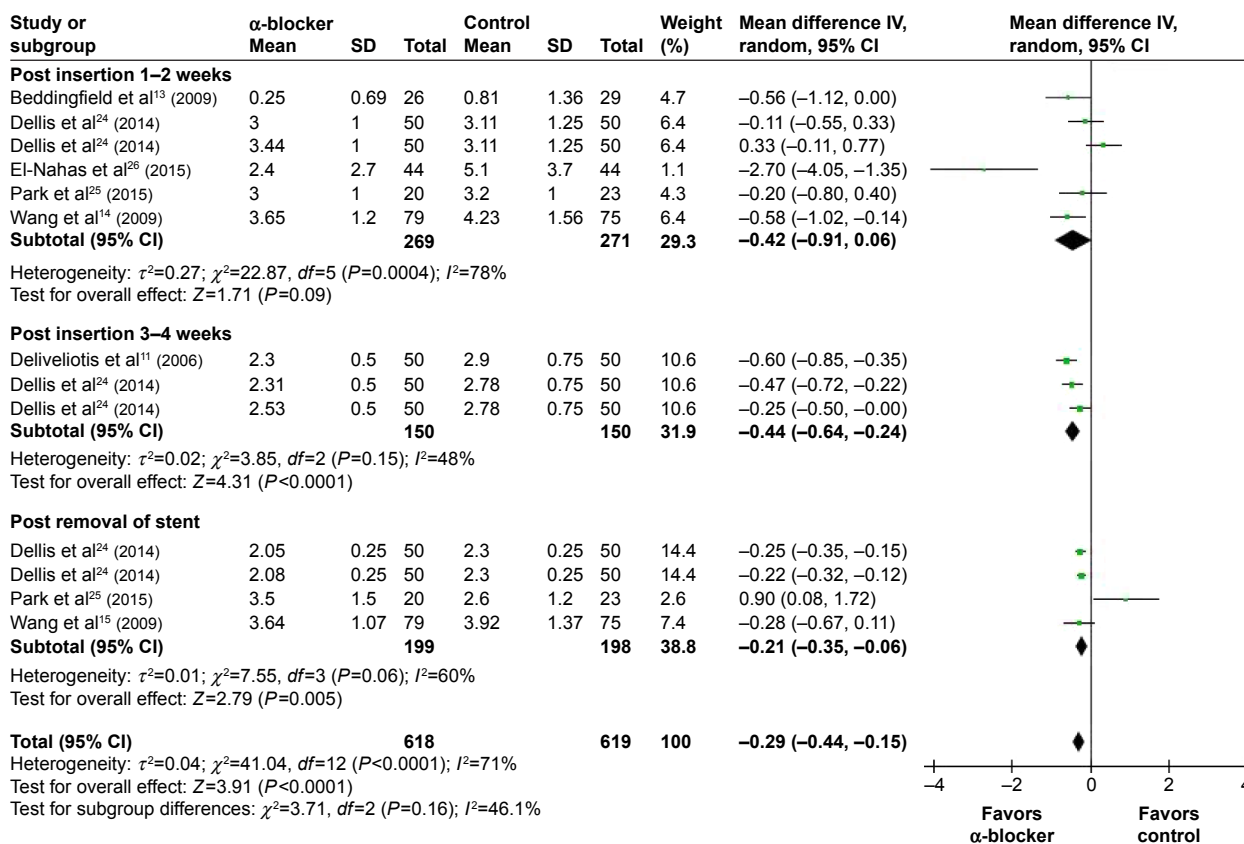**Abbreviations:** y, years; MD, mean difference; CI, confidence interval.

Study or subgroup	α-blocker Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI	Mean difference IV, random, 95% CI
Post insertion 1–2 weeks									
Beddingfield et al[13] (2009)	0.25	0.69	26	0.81	1.36	29	4.7	−0.56 (−1.12, 0.00)	
Dellis et al[24] (2014)	3	1	50	3.11	1.25	50	6.4	−0.11 (−0.55, 0.33)	
Dellis et al[24] (2014)	3.44	1	50	3.11	1.25	50	6.4	0.33 (−0.11, 0.77)	
El-Nahas et al[26] (2015)	2.4	2.7	44	5.1	3.7	44	1.1	−2.70 (−4.05, −1.35)	
Park et al[25] (2015)	3	1	20	3.2	1	23	4.3	−0.20 (−0.80, 0.40)	
Wang et al[14] (2009)	3.65	1.2	79	4.23	1.56	75	6.4	−0.58 (−1.02, −0.14)	
Subtotal (95% CI)			**269**			**271**	**29.3**	**−0.42 (−0.91, 0.06)**	

Heterogeneity: τ^2=0.27; χ^2=22.87, df=5 (P=0.0004); I^2=78%
Test for overall effect: Z=1.71 (P=0.09)

Post insertion 3–4 weeks									
Deliveliotis et al[11] (2006)	2.3	0.5	50	2.9	0.75	50	10.6	−0.60 (−0.85, −0.35)	
Dellis et al[24] (2014)	2.31	0.5	50	2.78	0.75	50	10.6	−0.47 (−0.72, −0.22)	
Dellis et al[24] (2014)	2.53	0.5	50	2.78	0.75	50	10.6	−0.25 (−0.50, −0.00)	
Subtotal (95% CI)			**150**			**150**	**31.9**	**−0.44 (−0.64, −0.24)**	

Heterogeneity: τ^2=0.02; χ^2=3.85, df=2 (P=0.15); I^2=48%
Test for overall effect: Z=4.31 (P<0.0001)

Post removal of stent									
Dellis et al[24] (2014)	2.05	0.25	50	2.3	0.25	50	14.4	−0.25 (−0.35, −0.15)	
Dellis et al[24] (2014)	2.08	0.25	50	2.3	0.25	50	14.4	−0.22 (−0.32, −0.12)	
Park et al[25] (2015)	3.5	1.5	20	2.6	1.2	23	2.6	0.90 (0.08, 1.72)	
Wang et al[15] (2009)	3.64	1.07	79	3.92	1.37	75	7.4	−0.28 (−0.67, 0.11)	
Subtotal (95% CI)			**199**			**198**	**38.8**	**−0.21 (−0.35, −0.06)**	

Heterogeneity: τ^2=0.01; χ^2=7.55, df=3 (P=0.06); I^2=60%
Test for overall effect: Z=2.79 (P=0.005)

Total (95% CI)			**618**			**619**	**100**	**−0.29 (−0.44, −0.15)**	

Heterogeneity: τ^2=0.04; χ^2=41.04, df=12 (P<0.0001); I^2=71%
Test for overall effect: Z=3.91 (P<0.0001)
Test for subgroup differences: χ^2=3.71, df=2 (P=0.16); I^2=46.1%

Favors α-blocker   Favors control

Figure 6 Meta-analysis results of sexual matters score.
Abbreviations: 95% CI, 95% confidence interval; *df*, degrees of freedom.

Additional problems score

Only two trials reported the mean additional problems score during post-insertion 1–2 weeks,[13,14] and meta-analysis result showed no significant difference between α-blockers and control (I^2=91%, MD =−1.50, 95% CI, −4.42, 1.43, P=0.32).

Quality of life score

Compared with control, α-blockers significantly decreased the mean quality of life score (I^2=96%, MD =−1.38, 95% CI, −1.96, −0.79, P<0.00001). Subgroup analysis according to outcome measured time showed that α-blockers significantly improved the quality of life score during post-insertion 1–2 weeks by a mean of −1.50 (95% CI, −2.39 to −0.62),[14,16,21,22,24,25] 3–4 weeks by a mean of −1.77 (95% CI, −3.11 to −0.42),[16,17,19,23,24] and post-removal by a mean of −0.44 (95% CI, −0.70 to −0.19).[24,25]

Others

Three trials reported data of patients with pain,[11,14,24] and their results showed that α-blockers significantly decreased the incidence of pain compared with control (36.68% vs 46.67%, I^2=0%, RR =0.78, 95% CI, −0.63, 0.97, P=0.03). Meta-analysis also revealed a superiority of α-blockers in aspects of irritative symptoms score (I^2=99%, MD =−5.43, 95% CI, −10.09, −0.77, P=0.02) and obstructive symptoms score (I^2=99%, MD =−4.27, 95% CI, −6.93, −1.61, P=0.002).

Discussion

As α-blockers were reported to be effective in the management after US insertion, many studies were conducted, and this study is an updated meta-analysis including the latest published articles. The study confirmed the efficacy of α-blockers in improving USSs, and, to our knowledge, it is also the first to qualitatively investigate the important clinical factors including stent duration, patient age, stent size, and α-blocker type, and to suggest the potential superiority of alfuzosin and terazosin compared to tamsulosin.

To judge the therapeutic effect of α-blockers, International Prostate Symptom Score (IPSS),[28] The Short-Form 36 Health Status Questionnaire (SF 36),[29] the EuroQol,[30] and the USSQ were used independently or complementarily in the included trials. Among them, USSQ was a self-administrated

multidimensional measure presented by Joshi et al[31] after they brought to attention the need for a validated questionnaire of USSs. It has proven to be a sensitive and stent-specific measuring tool.[32] Therefore, the meta-analysis mainly adopted items from USSQ as outcome measures to compare the efficacy of α-blocker in improving USSs.

Compared to control, additional administrated α-blockers significantly improved urinary symptom score and pain index score, and they had substantial positive effects on the general health index score, sexual matters score, pain incidence, irritative symptoms score, and obstructive symptoms score, but had no effect on work performance score and additional problems score. Previous studies had found an association between USSs and patients' quality of life,[32,33] and this study also indicated the association, as the improved quality of life score may be mainly contributed by the improved urinary symptom and pain index. Meanwhile, after including 16 RCTs of 1,489 cases, such a meta-analysis in random-effects models could, in a conservative manner, not only confirm the overall effects but also enable the investigation of clinical heterogeneity and different factors across the trials through the statistical methods of subgroup analysis and sensitive analysis.[34]

To investigate heterogeneity in the major outcome measures, first we omitted relatively low-quality trials, and the values of I^2 were to some extent reduced. Meanwhile, the outcome of urinary symptom score, pain index score, general health index, and sexual matters score did not obviously change, indicating a reliable and stable efficacy of α-blockers in improving USSQ. In order to ensure sufficiently statistical test power, an 80% power to detect a 15% difference in the urinary symptom score, a 30% difference in the pain index score, and a 25% difference in the general health index,[24] further subgroup and sensitivity analyses of outcome measured time, patient age, stent diameter, and α-blocker types were conducted based on a sample size of >50 patients in each group.

It has been reported that different durations of an indwelling stent would induce different influences on patients[35] and a longer duration can improve the overall tolerance.[5,6] Our study included trials with duration of stent insertion as well as drug administration from 8 days to 6 months, and researchers usually applied USSQ to patients one or more times during the period from insertion and even after removal. Therefore, considering the stent duration, drug administration, and measured time, a subgroup analysis during post-insertion 1–2 weeks, 3–4 weeks, and post-removal was primarily conducted. The results showed that α-blockers had a wide role

in improving both short-term and long-term USSs, and also had an effect even after stent removal, while they had little influence on short-term pain index, post-removal general health, and sexual matters.

As presented in the study of Wang et al,[14] patients with age >50 years had very different baseline IPSSs but similar USSQ compared with those aged ≤50 years. Regretfully, although the study distinguished sex (male/female) and age (<50/≥50 years), the authors did not make any comments on the issues. Confusingly, a rough analysis of three trials in our study showed that for patients ≥50 years α-blockers improved not urinary symptom score but sexual matters score.[11,14,25] Perhaps, the possibility of worse baseline condition of urinary symptoms in patients ≥50 years combined with additional burden of the stent was sometimes beyond the ability of the α-blocker.[36]

Some previous studies compared different stent diameters of 4.8F and 6F, and demonstrated that there was no significant difference in the aspects of pain, urinary symptoms, and quality of life, but the 4.8F stent was associated with a higher frequency of distal migration and dislodging.[37–39] However, the studies failed to reach the estimated sample size of 50 cases in each group, and our study revealed that patients with a stent ≥6F would suffer much more pain than with a stent <6F as α-blocker was found to fail to reduce the pain score index in the former cases.

Also, our meta-analysis is the first to investigate the difference between tamsulosin (a highly selective α-1A and α-1D adrenoceptor blocker) and other α-blockers including alfuzosin and terazosin (selective α-1 adrenoceptor blockers). Our results indicated that the latter achieved better improvement in the pain index and general health index score. In the absence of any elucidated mechanism of each symptom,[40] the difference between a highly selective α-1 blocker and a selective α-1 blocker may be due to the 1) the different location of α receptor in ureter and bladder trigone,[3,5] 2) the different pharmacological and physiological actions of α blockers and receptors, and 3) the different dosage and course of the drugs.

The limitations of our study are as follows. 1) In our study design, four of the included RCTs were of relatively poor quality and seven of them adopted a control other than placebo. 2) As mentioned above, many clinical factors and any underlying ureteral disease would have influenced the outcomes, and also different patient characteristics had a negative influence on the overall estimates. 3) Although different methods were used to identify and minimize the clinical factors, all these may still induce unavoidable heterogeneity

and bias. 4) As a study of positive results seems to be easier to get published than a negative one, publication bias might always exist. 5) For safety, as complications related to such α-blockers were stated to be mild and rare,[5] our study did not present much data on this. 6) Though the material and the site of stent distal end have been demonstrated to be very important factors,[41,42] our study did not involve the terms due to lack of information. 7) Finally, several recent studies have suggested that a combination therapy by α-blockers and antimuscarinic agents may be better than monotherapy with α-blockers alone, but due to lack of sufficient RCTs, our study did not involve this issue.

Conclusion

An α-blocker was found to be effective in treating USSs, as it improved the major indexes of USSQ post-insertion or post-removal. Alfuzosin and terazosin seemed to be better than tamsulosin, but this could not be verified due to lack of direct comparison studies currently.

Disclosure

The authors report no conflicts of interest in this work.

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