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RESEARCH ARTICLE

Adjunctive Medical Therapy with a-Blocker after Extracorporeal Shock Wave Lithotripsy of Renal and Ureteral Stones: A Meta-Analysis

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Abstract

Background

Although some trials assessed the efficacy and safety of the α -blocker in facilitating renal and ureteral stones expulsion after extracorporeal shock wave lithotripsy (ESWL), the role of the α -blocker in facilitating upper urinary calculi expulsion after ESWL remain controversial.

Aims

To determine the efficacy and safety of the α -blocker in facilitating renal and ureteral stones expulsion after ESWL.

Methods

A literature search was carried out using the PubMed database, EMBASE and the Cochrane Library database to identify relevant studies. Two reviewers independently extracted data and assessed methodological quality. Pooled effect estimates were obtained using a fixed- and random-effects meta-analysis.

Results

The meta-analysis included 23 RCTs, α -blocker significantly enhanced expulsion rate of upper urinary tract calculi after ESWL (P<0.00001; RR 1.21; 95% CI 1.12–1.31), significantly promoted steinstrasse expulsion (P=0.03; RR 1.25; 95% CI 1.03–1.53), significantly shortened the discharge time of upper urinary tract calculi (P=0.0001; MD -2.12; 95% CI -3.20–1.04), significantly reduced the patient's pain VAS score (P=0.001; RR -1.0; 95% CI -1.61–0.39). Compared with the control group, dizziness (P=0.002; RR 5.48; 95% CI 1.91–

15.77), anejaculation (P=0.02; RR 12.17; 95% Cl 1.61–91.99) and headache (P=0.04; RR 4.03; 95% Cl 1.04–15.72) in the α -blocker group was associated with a higher incidence.

Conclusions

Treatment with α -blocker after ESWL appears to be effective in enhancing expulsion rate of upper urinary tract calculi, shortening the discharge time of upper urinary tract calculi, reducing the patient's pain. The side effects of α -blocker were light and few.

Introduction

Urolithiasis has plagued human beings for thousands of years [1]. Urolithiasis is a disease that affects 8–15% of the population of Europe and North America [2]. Extracorporeal shock wave lithotripsy (ESWL) was introduced by Chaussy et al in the 1980s [3]. Today, about 80% of urinary tract stones are managed with ESWL. Initially a treatment for renal and upper ureteric stones, it soon became clear that ESWL could also be used to treat stones within the middle and distal ureter [4]. ESWL produces fragmentation of the calculi using shockwaves and facilitates calculi elimination through the excretory pathway, is currently the initial treatment of choice for uncomplicated stones located in the upper urinary tract [5]. Success rates of ESWL depend on the type of lithotripter used, stones size and location [6]. In recent years, new treatments have been developed aiming to further improve the success rate after ESWL. Medical expulsion therapy, which includes α -blocker, and conventional analgesic and anti-inflammatory drugs, has shown promise in accelerating the spontaneous clearance of urinary stones as well as adjunctive treatment after ESWL for urinary stones [7].

More recent studies evaluated effect of α -blocker after ESWL on urinary stones clearance, but the evidence for their effectiveness in assisting stones clearance remained conflicting. A meta-analysis combining the studies reported to date would provide information about effect of α -blocker. The direction and magnitude of this effect will help in guiding decisions about clinical practice.

Methods

Search strategy

The literature search was undertaken according to the guidelines of the Centre for Reviews and Dissemination and Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [8]. An extensive PubMed, EMBASE, and The Cochrane Library search was performed including the following terms: α -blocker (or α -adrenergic antagonist, or α receptor antagonist, or tamsulosin, or doxazosin, or alfuzosin, or terazosin), and SWL (or ESWL, or shock wave lithotripsy, or shockwave lithotripsy, or ultrasonic lithotripsy, or lithotripter). We considered all publications in any language published before February 28, 2014.

Study selection

The studies that met the following criteria were included: (1) RCTs; (2) patients with renal and/or ureteric calculi who were treated with ESWL; (3) α -blocker as an intervention compared with placebo or a control group; (4) Outcome measures that should be reported were clearance rate or pain (VAS) or expulsion time. Exclusion criteria were: trials in which

combined intervention of α -blocker with other proven spasmolytics (e.g. corticosteroids, calcium channel blockers and phloroglucinol) were applied.

Data abstraction and quality assessment

The abstraction of data was conducted by two independent investigators. Discrepancies were resolved by discussion and simultaneous reference to the relevant literatures. The methodological quality of the included trials was evaluated using the Jadad quality scale [9]: (1) randomization (the study was described as randomized); (2) double blinding (participant masking and researcher masking); (3) reporting of the number of dropouts and reasons for withdrawal; (4) allocation concealment; (5) generation of random numbers (by using computer, random numbers table, shuffled cards, or tossed coins). RCTs scored 1 point for each area addressed in the study design for a possible score between 0 and 5 (highest level of quality). The quality of all included studies was assessed by two investigators and the articles were classified as high-quality if their Jadad score \geq 4 and low quality if their Jadad score \leq 3. Disagreements regarding methodological quality were resolved with discussion between reviewers.

Statistical analysis

Meta-analyses and forest plots were carried out by the use of Review Manager version 5.3 software. RR and 95% CI were calculated for the expulsion rate of stones and incidence of side effects during treatment. Weighted mean differences and 95% CI were for expulsion time and Pain. Heterogeneity was assessed using the I-square test. When heterogeneity was present (I-square >25%) the data was analyzed using the random-effects model, otherwise a fixed-effect was used. For all studies analyzed, a P-value of less than 0.05 was considered statistically significant. Publication bias was explored via a funnel-plot analysis. The Begg rank correlation and Egger weighted regression test methods were also used to statistically assess publication bias by Stata 12.0 (P<0.05 was consider as indicative of statistically significant publication bias). In case of heterogeneity, subgroup analysis was conducted according to dosage of drug, different stone size and location.

Results

Study selection and characteristics

Our search strategy identified 236 studies, through an abstract review we excluded all references related to other topics, editorials, alternate study designs (ie observational studies), duplicate references, reviews and review articles, of which 24 were potentially relevant trials (Fig 1). One [10] was excluded for combined intervention of α -blocker with phloroglucinol (spasmolytic drug) resulting in a total of 23 RCTs [11–33] which met study criteria. The characteristics and results of the 23 included studies are summarized in Table 1.

The mean Jadad score of these 23 studies was 3.2, ranging from 1 to 5 points (Table 2). 8 of 23 RCTs met the Jadad criteria for high quality [12], [14], [16], [19]-[20], [22], [27], [29]. All of the studies included suggested randomization, and 14 studies reported the method of random sequences generation [12], [14]-[20], [22], [24], [27]-[29], [33]. Double blinded method were used only in four studies [12], [14], [16], [22], we considered that the outcomes and their measurements may likely to be influenced by lack of blinding. In general, the methodological and report qualities of the included studies were good, but still not very ideal.



Fig 1. Study selection process for trials included in meta-analysis.

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Statistical results

The expulsion rate of α -blocker for stones. The expulsion rate was analyzed in 22 of the 23 studies. The expulsion rate of the α -blocker group was significant higher than that of the control group (P<0.00001; RR 1.21; 95% CI 1.12–1.31) (Fig 2). The expulsion rate of the tamsulosin 0.4mg group was analyzed in 16 of the 23 studies. The expulsion rate of the tamsulosin 0.4mg group was significant higher than that of the control group (P<0.00001; RR 1.28; 95% CI 1.16-1.42) (Fig 3), there was no significant difference in the expulsion rate between tamsulosin 0.2mg group and control group (P = 0.57; RR 1.09; 95% CI: 0.81–1.47) (Fig 3). The expulsion rate of the α -blocker group was significant higher than that of the control group both for renal stones (P<0.0001; RR 1.34; 95% CI 1.16–1.55) and ureteral stones (P = 0.002; RR 1.20; 95% CI 1.07–1.35) (Fig 4). The expulsion rate of the α -blocker group was significant higher than that of the control group both for lower ureteral stones (P = 0.008; RR 1.29; 95% CI 1.07– 1.56) and upper ureteral stones (P = 0.005; RR 1.14; 95% CI: 1.04–1.25) (Fig.5). The expulsion rate of the α -blocker group was higher than that of the control group for 4–10 mm stones (P = 0.01; RR 1.10; 95% CI: 1.02–1.19), 10–20 mm stones (P<0.00001; RR 1.76; 95% CI: 1.47– 2.10) and 10-30 mm stone (P = 0.006; RR 1.55; 95% CI: 1.14-2.12) (Fig 6). The expulsion rate of the α -blocker group was significant higher than that of the control group for steinstrasse (Fig 7) (P = 0.03; RR 1.25; 95% CI: 1.03–1.53).



Table 1. The characteristics and results of the 23 included studies.

Author (year)	Region	Subgroup	Mean age (years)	Male: female	No. patients	Stone location	Stone size range (mm)
Wang (2009)	Taiwan	TG	-	44:25	69	LU	-
		CG	51.98±8.9	25:13	38	LU	6.5±1.2
Vicentini (2011)	Brazil	TG	47.3±11.5	16:22	38	Renal	10 (5–20)
		CG	45.7±15.1	24:14	38	Renal	12 (6–20)
Georgiev (2011)	Bulgaria	TG	54±20	67:32	99	U, R	10±4,14±6
		CG	51±22	54:33	87	U, R	9±5,12±7
Falahatkar (2011)	Iran	TG	45.5±14	53:22	75	U, R	13.22
		CG	47±14	52:23	75	U, R	12.88
Agarwal (2009)	India	TG	32.4±8.7	15:5	20	UU	9.4±1.9
		CG	35.5±15.4	16:4	20	UU	10.4±3
Singh (2011)	India	TG	32.2±12.22	44:15	59	UU	-
		CG	36±13.78	41:17	58	UU	-
Resim (2005)	Turkey	TG	39(21–55)	21:11	32	LU	21(10–30)
		CG	37(23–57)	22:13	35	LU	20(10–26)
Moursy (2010)	Egypt	TG	35.6±9.95	28:16	44	U	6.39±0.99
		CG	33.9±9.71	27:17	44	U	6.07±1.18
Cakıroglu (2013)	Turkey	TG	44.66±13.25	47:12	59	U	11.40±3.01
,		CG	42.19±13.17	51:13	64	U	10.70±3.2
KÜPELI (2004)	Turkey	TG	-	-	39	LU	-
		CG		-	39	LU	-
Micali(2007)	Italy	TG	45(27–71)	16:12	28	LU	10.25±1.35
· · ·	,	CG	46(25-72)	11:10	21	LU	9.9±1.37
Bhagat (2006)	India	TG	35.9±7.8	22:7	29	U, R	-
		CG	42.3±12.3	24:5	29	U. R	-
Kobavashi (2008)	Japan	TG	57.76±8.69	-	38	U	10.61±4.45
(,		CG	52.29±14.63	-	34	U	9.85±3.13
Naia (2008)	India	TG	37.17±12.59	36:15	51	R	12.12±3.59
- J ()		CG	39.44±14.49	43:22	65	В	13.06±3.49
Gravas (2007)	Greece	TG	48.8 (27–73)	18:12	30	LU	8.5 (6–13)
		CG	49.2 (30–72)	20:11	31	LU	8.3 (6–12)
Wang (2008)	China	TG	39.7+11.6	31:9	40	10	8.6+2.6
114.1g (2000)	e i i i i i	CG	38.5+9.5	28:12	40	10	8.2+3.1
Ates (2012)	Turkey	TG	38.35+11.41	25:10	35	UU	9.06+1.45
, (_0, _)	. antoy	CG	30 95+9 68	33.11	44	UU	8 30+2 51
Janane (2014)	Morocco	TG	41.2 + 12.4	108:78	186		9.2 + 2.8
		CG	43.4 + 12.2	104:66	170	10	9.4 + 3.0
Hussein (2010)	Favot	TG	44 (27–62)	40.27	67	B	-
	-9)pt	CG	40 (20-60)	45:24	69	B	_
Gul (2013)	Turkey	TG	63 2+6 7	-	34	UB	12 6+5 3
0.0. (20.0)	. antoy	CG	58 6+7 2	-	230	UR	13 3+4 7
Wang (2010)	China	TG	42 2+12 6	36.19	54		9 3+2 6
Wang (2010)	Offinia	CG	40.9+10.3	38.14	52	111	8 6+3 0
Cho (2012)	Korea	TG	47 4+12 6	29.12	41	11	7 1+1 7
	Noica	CG	47 7+12 1	31.12	43	U U	7 2+1 8
Park (2013)	Korea	TG	46.2	29:15	44		9.2
- and (2010)	Norda	CG	47.6	28.16	44		9.6
		00	47.0	20.10		00	0.0

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Author (year)	Randomization	Double blinding	Withdrawal or drop-out	Total Jadad score (possible total = 5)
Wang (2009)	1	0	1	2
Vicentini (2011)	2	2	1	5
Georgiev (2011)	1	0	1	2
Falahatkar (2011)	2	2	1	5
Agarwal (2009)	2	0	1	3
Singh (2011)	2	2	1	5
Resim (2005)	2	0	1	3
Moursy (2010)	2	0	1	3
Cakıroglu (2013)	2	1	1	4
KÜPELI (2004)	2	1	1	4
Micali(2007)	1	1	1	3
Bhagat (2006)	2	2	1	5
Kobayashi (2008)	1	1	1	3
Naja (2008)	2	0	1	3
Gravas (2007)	1	1	1	3
Wang (2008)	1	0	1	2
Ates (2012)	2	1	1	4
Janane (2014)	2	0	1	3
Hussein (2010)	2	1	1	4
Gul (2013)	1	0	0	1
Wang (2010)	1	0	0	1
Cho (2012)	1	1	1	3
Park (2013)	2	0	1	3

Table 2. Jadad Trial Quality Scores.

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The expulsion time of the α-blocker for stones. The expulsion time of the α-blocker group was analysed in 12 of the 23 studies. The expulsion time of the α-blocker group was significant shorter than that of the control group for renal and ureteral stones (P = 0.0001; MD -2.12; 95% CI -3.20--1.04) (Fig.8). The expulsion time of the tamsulosin 0.4mg group was analysed in 9 of the 23 studies. The expulsion time of the tamsulosin 0.4mg group was significant shorter than that of the control group (P<0.00001; MD -2.46; 95% CI -3.46--1.46) (Fig.8). The expulsion time of the tamsulosin 0.4mg group was significant shorter than that of the control group (P<0.00001; MD -2.46; 95% CI -3.46--1.46) (Fig.8). The expulsion time of the α-blocker group was significant shorter than that of the control group for ureteral stones (P = 0.002; MD -1.90; 95% CI -3.09--0.72) (Fig.9). There was no significant difference in the expulsion time between α-blocker group and control group both for upper ureteral stones (P = 0.38; MD -2.13 95% CI -6.87-2.62) and lower ureteral stones (P = 0.26; MD -1.23; 95% CI -3.36-0.89) (Fig.9).

Pain. The difference in VAS (visual analogue scale, VAS) score between the α -blocker group and control group showed statistical significance (P = 0.001; MD -1.0; 95% CI -1.61--0.39) (Fig 10).

Proportion of patients with renal or ureteral colic of the α -blocker group was significant less than that of control group during treatment (P<0.00001; RR 0.3; 95% CI 0.22–0.40) (Fig 10).

Incidence of side effects during treatment. The frequencies of any adverse event are shown in Fig 11, compared with the control group, dizziness (P = 0.002; RR 5.48; 95% CI 1.91– 15.77), anejaculation (P = 0.02; RR 12.17; 95% CI 1.61–91.99) and headache (P = 0.04; RR 4.03; 95% CI 1.04–15.72) in the α -blocker group was associated with a higher incidence.



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	α-bloc	ker	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Agarwal 2009	19	20	18	20	5.4%	1.06 [0.88, 1.26]	
Ates, 2012	33	35	35	44	5.6%	1.19 [1.00, 1.41]	
Bhagat 2006	28	29	23	29	5.1%	1.22 [1.00, 1.48]	
Cho 2013	39	41	40	43	6.7%	1.02 [0.92, 1.14]	+
Falahatkar 2011	50	70	43	71	4.4%	1.18 [0.93, 1.50]	+
Georgiev 2011	90	99	65	87	6.2%	1.22 [1.06, 1.40]	
Gravas 2007	19	30	16	31	2.1%	1.23 [0.79, 1.90]	
Gul 2013	30	34	165	230	6.0%	1.23 [1.06, 1.42]	
Hussein 2010	49	67	38	69	4.1%	1.33 [1.03, 1.72]	
Janane 2014	144	186	82	170	5.5%	1.61 [1.35, 1.91]	
Kobayashi 2008	32	38	30	34	5.3%	0.95 [0.79, 1.15]	
KÜPELI 2004	17	24	8	24	1.2%	2.13 [1.14, 3.96]	
Micali 2007	23	28	12	21	2.4%	1.44 [0.96, 2.16]	
Moursy 2010	32	44	25	44	3.3%	1.28 [0.93, 1.75]	+
Naja 2008	48	51	49	65	5.9%	1.25 [1.07, 1.46]	
Park 2013	37	44	29	44	4.2%	1.28 [1.00, 1.64]	
Resim 2005	24	32	23	35	3.3%	1.14 [0.84, 1.56]	
Singh 2011	54	59	50	58	6.4%	1.06 [0.93, 1.21]	+
Vicentini 2011	23	38	14	38	1.8%	1.64 [1.01, 2.68]	
Wang 2008	31	40	18	40	2.6%	1.72 [1.18, 2.52]	
Wang 2009	28	35	31	38	4.6%	0.98 [0.78, 1.23]	
Wang 2009	29	34	31	38	4.9%	1.05 [0.85, 1.28]	
Wang 2010	41	55	24	52	3.1%	1.62 [1.16, 2.25]	
Total (95% CI)		1133		1325	100.0%	1.21 [1.12, 1.31]	◆
Total events	920		869				
Heterogeneity: Tau ² =	0.02; Ch	i ² = 61.1	20, df = 2	2 (P < 0	0.0001): P	² = 64%	
Test for overall effect:	Z = 5.01	(P < 0.0	0001)				U.2 U.5 1 2 5
							Favours [Control] Favours (α-blocker]

Fig 2. The expulsion rate of the α -blocker.

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Publication bias analysis

The distribution of the studies using traditional funnel plot (Fig 12) showed asymmetrical distribution of effect estimate, which suggested the possibility of publication bias. Egger weighted regression analysis (p = 0.027) also showed presence of publication bias. But the Begg rank correlation statistic (p = 0.428) showed no evidence of publication bias.

Discussion

This meta-analysis suggested that α -blocker significantly enchanced the expulsion rate of upper urinary tract calculi and steinstrasse, shortened stones expulsion time, reduced the pain of patients. Side effects of α - blocker was light and few.

The expulsion rate of the tamsulosin

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	Tamsulo	osin	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.2.1 0.4mg Tamsulo	sin VS Co	ntrol					
Agarwal 2009	19	20	18	20	7.4%	1.06 [0.88, 1.26]	
Bhagat 2006	28	29	23	29	7.0%	1.22 [1.00, 1.48]	
Falahatkar 2011	50	70	43	71	6.2%	1.18 [0.93, 1.50]	+
Gravas 2007	19	30	16	31	3.3%	1.23 [0.79, 1.90]	
Hussein 2010	49	67	38	69	5.8%	1.33 [1.03, 1.72]	
Janane 2014	144	186	82	170	7.5%	1.61 [1.35, 1.91]	
KÜPELI 2004	17	24	8	24	1.9%	2.13 [1.14, 3.96]	
Micali 2007	23	28	12	21	3.6%	1.44 [0.96, 2.16]	
Moursy 2010	32	44	25	44	4.8%	1.28 [0.93, 1.75]	
Naja 2008	48	51	49	65	7.9%	1.25 [1.07, 1.46]	
Resim 2005	24	32	23	35	4.9%	1.14 [0.84, 1.56]	
Singh 2011	54	59	50	58	8.4%	1.06 [0.93, 1.21]	+-
Vicentini 2011	23	38	14	38	2.8%	1.64 [1.01, 2.68]	
Wang 2008	31	40	18	40	3.9%	1.72 [1.18, 2.52]	
Wang 2009	29	34	31	38	6.8%	1.05 [0.85, 1.28]	_ _
Wang 2010	41	55	24	52	4.6%	1.62 [1.16, 2.25]	
Subtotal (95% CI)		807		805	86.7%	1.28 [1.16, 1.42]	•
Total events	631		474				
Heterogeneity: Tau ² =	0.02; Chi ²	= 38.6	4, df = 15	(P = 0	.0007); I ²	= 61%	
Test for overall effect:	Z = 4.77 (F	P < 0.00	0001)				
1 2 2 0 2mg Tomoulo		ntrol					
1.2.2 0.2mg Tamsulo	SIII VS CO		20		7.00	0.05 (0.70, 4.45)	
Kobayashi 2008	32	38	30	34	1.3%	0.95 [0.79, 1.15]	
Park 2013 Subtatal (05% CI)	31	44	29	44	0.0%	1.28 [1.00, 1.64]	
Subtotal (95% CI)	~~	82	50	78	15.5%	1.09[0.81, 1.47]	
Total events	09		59				
Heterogeneity: I au* =	0.03; Chi	= 3.76	, af = 1 (⊦	' = 0.05); h= 739	8	
lest for overall effect:	Z= 0.57 (ł	² = 0.57)				
Total (95% CI)		889		883	100.0%	1.25 [1.14, 1.38]	◆
Total events	700		533				
Heterogeneity: Tau ² =	0.02; Chi ²	= 46.6	9, df = 17	(P = 0	.0001); l²	= 64%	
Test for overall effect:	Z = 4.60 (F	P < 0.00	0001)				Eavours [Control] Eavours [Tameulosin]
Test for subaroup diff	erences: C	chi² = 0	98. df = 1	1 (P = 0	.32). I ² =	0%	

Fig 3. The expulsion rate of tamsulosin.

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This meta-analysis included 23 RCTs [11]-[33], with 979 patients in experimental group, 933 patients in control group. Heterogeneity existed in expulsion rate of upper urinary tract calculi, the reason for heterogeneity might relate to ESWL energy and frequency, the location and the size of the stones. When separately analyzed ureter calculi, renal stones, 4–10 mm stones, we did not observe heterogeneity.

We observed a significant improvement in the success rates for the adjuvant use of α -blockers for ureteral stones, upper and lower ureteral stones, renal stones, 4–10 mm stones, 10–20 mm stones, 10–30mm stones. α -blocker could significantly promote steinstrasse discharge. A previous meta-analysis [6] excluded steinstrasse, our meta-analysis for the first time showed that α -blockers could significantly promoted steinstrasse discharge.



The expulsion rate of the α -blocker for renal stones

	α-bloc	ker	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Hussein 2010	49	67	38	69	39.6%	1.33 [1.03, 1.72]	
Naja 2008	48	51	49	65	45.6%	1.25 [1.07, 1.46]	
Vicentini 2011	23	38	14	38	14.8%	1.64 [1.01, 2.68]	
Total (95% CI)		156		172	100.0%	1.34 [1.16, 1.55]	◆
Total events	120		101				
Heterogeneity: Chi ² =	1.45, df =	2 (P =	0.48); l ² =	= 0%			
Test for overall effect:	Z = 3.90 ((P < 0.0	001)				Favours [Control] Favours [α-blocker]

The expulsion rate of the α -blocker for ureteral stones

	α-bloc	ker	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Agarwal 2009	19	20	18	20	8.1%	1.06 [0.88, 1.26]	
Ates, 2012	33	35	35	44	8.2%	1.19 [1.00, 1.41]	
Cho 2013	39	41	40	43	9.2%	1.02 [0.92, 1.14]	+
Gravas 2007	19	30	16	31	4.2%	1.23 [0.79, 1.90]	
Janane 2014	144	186	82	170	8.2%	1.61 [1.35, 1.91]	
Kobayashi 2008	32	38	30	34	8.0%	0.95 [0.79, 1.15]	
KÜPELI 2004	17	24	8	24	2.6%	2.13 [1.14, 3.96]	
Micali 2007	23	28	12	21	4.5%	1.44 [0.96, 2.16]	
Park 2013	37	44	29	44	6.9%	1.28 [1.00, 1.64]	
Resim 2005	24	32	23	35	5.9%	1.14 [0.84, 1.56]	- _
Singh 2011	54	59	50	58	8.9%	1.06 [0.93, 1.21]	+
Wang 2008	31	40	18	40	4.9%	1.72 [1.18, 2.52]	· · · · · · · · · · · · · · · · · · ·
Wang 2009	28	35	31	38	7.3%	0.98 [0.78, 1.23]	
Wang 2009	29	34	31	38	7.6%	1.05 [0.85, 1.28]	
Wang 2010	41	55	24	52	5.6%	1.62 [1.16, 2.25]	
Total (95% CI)		701		692	100.0%	1.20 [1.07, 1.35]	◆
Total events	570		447				
Heterogeneity: Tau² =	0.04; Ch	i ² = 60.	18, df = 1	4 (P < I	0.00001);	I ² = 77%	
Test for overall effect:	Z = 3.08	(P = 0.0	02)				Favours [Control] Favours [α-blocker]
Fig 4. The expulsion rat	te of the a	-block	er for ren	al and u	ureteral s	tones.	

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Our meta-analysis from studies suggested that α -blockers could significantly shorten the discharge time of upper urinary tract stones and ureteral stones, but there was heterogeneity among these studies. The reason for heterogeneity might relate to difference of drug treatment time, ESWL energy and frequency, the location and the size of the stones. α -blocker shorten upper and lower ureteral stones discharge time, but without statistical significance, which might be related to the size and location of the stones.

Tamsulosin was used as adjuvant therapy in 20 studies, of which 18 was tamsulosin 0.4mg [11]-[12], [14]-[18], [20]-[22], [24]-[26], [28]-[29], [31], of which 2 was tamsulosin 0.2mg, one



The expulsion rate of the α -blocker for upper ureteral stones

	α-bloc	ker	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Agarwal 2009	19	20	18	20	14.0%	1.06 [0.88, 1.26]]
Ates, 2012	33	35	35	44	24.1%	1.19 [1.00, 1.41]] –
Park 2013	37	44	29	44	22.6%	1.28 [1.00, 1.64]	
Singh 2011	54	59	50	58	39.3%	1.06 [0.93, 1.21]	i 🗕
Total (95% CI)		158		166	100.0%	1.14 [1.04, 1.25]	1 ◆
Total events	143		132				
Heterogeneity: Chi ² =	2.86, df=	3 (P =	0.41); l ² =	= 0%			
Test for overall effect:	Z = 2.81	(P = 0.0)05)				U.2 U.5 I 2 5 Favours [Control] Favours [α-blocker]

The expulsion rate of the α -blocker for lower ureteral stones

	a-bloc	ker	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Gravas 2007	19	30	16	31	10.1%	1.23 [0.79, 1.90]	
KÜPELI 2004	17	24	8	24	6.5%	2.13 [1.14, 3.96]	
Micali 2007	23	28	12	21	10.8%	1.44 [0.96, 2.16]	
Resim 2005	24	32	23	35	13.7%	1.14 [0.84, 1.56]	
Wang 2008	31	40	18	40	11.6%	1.72 [1.18, 2.52]	
Wang 2009	29	34	31	38	17.4%	1.05 [0.85, 1.28]	
Wang 2009	28	35	31	38	16.8%	0.98 [0.78, 1.23]	
Wang 2010	41	55	24	52	13.1%	1.62 [1.16, 2.25]	
Total (95% CI)		278		279	100.0%	1.29 [1.07, 1.56]	◆
Total events	212		163				
Heterogeneity: Tau ² =	0.04; Ch	i ² = 18.	08, df = 7	(P = 0.	01); I ² = 6	1% –	
Test for overall effect:	Z = 2.67	(P = 0.0)08)			0.	Favours [Control] Favours [α-blocker]

Fig 5. The expulsion rate of the α -blocker for upper and lower ureteral stones.

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of which was from Japan [23], another of which was from South Korea [33]. Tamsulosin 0.4 mg significantly promoted the discharge of upper urinary tract stones, significantly shorten the discharge time of stones. However, tamsulosin 0.2 mg could not significantly promote the ure-teral stones expulsion, however, the result only from two studies, this need a large number of clinical trials to confirm.

 α -blockers can significantly reduce the patient's pain and the proportion of patients with renal colic. In some studies, a total VAS score was 100points, in some studies, a total VAS score was 10 points, in order to facilitate statistical analysis, we took 100 points as the total score of data conversion into total score of 10 points data.

Side effect of α -blockers was light and few, the common side effects were headache, dizziness, majority of which was mild dizziness, anejaculation. In the treatment group, one patient experienced delay ejaculation, one patient experienced abnormal ejaculation, one patient



The expulsion rate of the α -blocker for 4-10mm stones

	a-bloc	ker	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Bhagat 2006	14	14	16	17	6.3%	1.05 [0.89, 1.25]	_ +•
Cho 2013	39	41	40	43	16.4%	1.02 [0.92, 1.14]	_ + _
Janane 2014	64	83	44	68	20.4%	1.19 [0.96, 1.47]	+
Park 2013	37	44	29	44	12.2%	1.28 [1.00, 1.64]	
Singh 2011	28	30	27	30	11.4%	1.04 [0.89, 1.21]	
Vicentini 2011	10	17	8	15	3.6%	1.10 [0.59, 2.05]	
Wang 2009	28	35	31	38	12.5%	0.98 [0.78, 1.23]	
Wang 2009	29	34	31	38	12.3%	1.05 [0.85, 1.28]	
Wang 2010	14	18	12	19	4.9%	1.23 [0.81, 1.88]	
Total (95% CI)		316		312	100.0%	1.10 [1.02, 1.19]	◆
Total events	263		238				
Heterogeneity: Chi ² = I	6.18, df=	8 (P =	0.63); I ² =	: 0%			
Test for overall effect:	Z = 2.46	(P = 0.0	01)				Favours [Control] Favours [α-blocker]

The expulsion rate of the α -blocker for 10-20mm stones

	α-bloc	ker	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Janane 2014	80	103	40	102	49.0%	1.98 [1.52, 2.58]]
Singh 2011	26	29	23	28	28.5%	1.09 [0.88, 1.35]	ı] — <mark> ■</mark> —
Vicentini 2011	13	21	6	23	7.0%	2.37 [1.10, 5.10]	g
Wang 2010	27	37	12	33	15.5%	2.01 [1.23, 3.28]	.j — —
Total (95% CI)		190		186	100.0%	1.76 [1.47, 2.10]	1 ◆
Total events	146		81				
Heterogeneity: Chi ² =	21.02, df	= 3 (P =	= 0.0001)); l ² = 88	6%		
Test for overall effect:	Z= 6.24	(P < 0.0	00001)				Favours [Control] Favours [α-blocker]

The expulsion rate of the α -blocker for 10-30mm stones

	α-bloc	ker	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Bhagat 2006	14	15	7	12	14.8%	1.60 [0.97, 2.63]	
Janane 2014	80	103	40	102	20.2%	1.98 [1.52, 2.58]	_
Resim 2005	24	32	23	35	19.1%	1.14 [0.84, 1.56]	_
Singh 2011	26	29	23	28	21.3%	1.09 [0.88, 1.35]	
Vicentini 2011	13	21	6	23	9.7%	2.37 [1.10, 5.10]	
Wang 2010	27	37	12	33	14.9%	2.01 [1.23, 3.28]	
Total (95% CI)		237		233	100.0%	1.55 [1.14, 2.12]	◆
Total events	184		111				
Heterogeneity: Tau ² =	0.11; Ch	i ² = 22.	29, df = 5	(P = 0.	0005); I ² :	= 78%	
Test for overall effect:	Z= 2.76	(P = 0.0)06)				Favours [Control] Favours [α-blocker]

Fig 6. The expulsion rate of the $\alpha\mbox{-blocker}$ for different size stones.

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The expulsion rate of the α -blocker for steinstrasse

	Tamsul	osin	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Bhagat 2006	10	10	6	8	12.7%	1.32 [0.86, 2.02]	
Moursy 2010	32	44	25	44	44.5%	1.28 [0.93, 1.75]	+
Resim 2005	24	32	23	35	39.1%	1.14 [0.84, 1.56]	
Vicentini 2011	5	5	1	2	3.6%	1.83 [0.58, 5.83]	
Total (95% CI)		91		89	100.0 %	1.25 [1.03, 1.53]	◆
Total events	71		55				
Heterogeneity: Chi ² =	0.84, df=	3 (P = (0.84); I ² =	0%			
Test for overall effect:	Z = 2.21 (P = 0.03	3)				Favours [Control] Favours [Tamsulosin]

Fig 7. The expulsion rate of the $\alpha\mbox{-blocker}$ for steinstrasse.

doi:10.1371/journal.pone.0122497.g007

The expulsion time of the α -blocker for renal and ureteral stones

	α-blocker Control							Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Agarwal 2009	30.7	19.6	20	39	19.9	20	0.7%	-8.30 [-20.54, 3.94]	
Ates, 2012	4.14	1.78	35	3.61	2.71	44	12.9%	0.53 [-0.46, 1.52]	t
Cakıroglu 2013	8.34	7.6	59	12.59	8.63	64	7.2%	-4.25 [-7.12, -1.38]	-
Cho 2013	9.5	4.8	41	18.6	20.6	43	2.4%	-9.10 [-15.43, -2.77]	
Gravas 2007	12.95	6.92	30	13.22	4.73	31	6.9%	-0.27 [-3.25, 2.71]	-
Janane 2014	8.4	1.8	186	10.6	1.6	170	14.3%	-2.20 [-2.55, -1.85]	•
Kobayashi 2008	15.66	6.14	38	35.47	53.7	34	0.3%	-19.81 [-37.97, -1.65]	
Moursy 2010	12.67	2.29	44	15.07	3.55	44	12.2%	-2.40 [-3.65, -1.15]	+
Naja 2008	35.53	19.47	51	47.22	23.64	65	1.7%	-11.69 [-19.54, -3.84]	
Singh 2011	26.78	11.96	59	31.28	18.31	58	3.0%	-4.50 [-10.11, 1.11]	2
Wang 2009	6.1	2.3	34	6.5	2.7	38	12.5%	-0.40 [-1.56, 0.76]	+
Wang 2009	6.2	3	35	6.5	2.7	38	12.0%	-0.30 [-1.61, 1.01]	+
Wang 2010	8.1	1.6	55	11.6	1.4	52	14.0%	-3.50 [-4.07, -2.93]	•
Total (95% CI)			687			701	100.0%	-2.12 [-3.20, -1.04]	•
Heterogeneity: Tau ² =	2.09; C	hi² = 85.	.36, df=	= 12 (P	< 0.000	01); I ² =	86%		
Test for overall effect:	Z= 3.84	(P = 0.1	0001)						-20 -10 0 10 20 Favours (α-blocker) Favours (control)

The expulsion time of the tamsulosin 0.4mg for renal and ureteral stones

	Tamsulosin Control							Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Agarwal 2009	30.7	19.6	20	39	19.9	20	0.6%	-8.30 [-20.54, 3.94]	
Cakıroglu 2013	8.34	7.6	59	12.59	8.63	64	8.0%	-4.25 [-7.12, -1.38]	
Gravas 2007	12.95	6.92	30	13.22	4.73	31	7.6%	-0.27 [-3.25, 2.71]	
Janane 2014	8.4	1.8	186	10.6	1.6	170	22.8%	-2.20 [-2.55, -1.85]	•
Moursy 2010	12.67	2.29	44	15.07	3.55	44	17.1%	-2.40 [-3.65, -1.15]	+
Naja 2008	35.53	19.47	51	47.22	23.64	65	1.5%	-11.69 [-19.54, -3.84]	
Singh 2011	26.78	11.96	59	31.28	18.31	58	2.8%	-4.50 [-10.11, 1.11]	
Wang 2009	6.1	2.3	34	6.5	2.7	38	17.8%	-0.40 [-1.56, 0.76]	+
Wang 2010	8.1	1.6	55	11.6	1.4	52	21.8%	-3.50 [-4.07, -2.93]	•
Total (95% CI)			538			542	100.0%	-2.46 [-3.46, -1.46]	•
Heterogeneity: Tau ² =	1.10; C	hi² = 37.	39, df :	= 8 (P <	0.0000	1); I ² = 7	79%	-	
Test for overall effect:	Z= 4.84	(P < 0.0	00001)						-20 -10 0 10 20
									Favours (ramsulosin) Favours (Control)

Fig 8. The expulsion time of the α -blocker.

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The expulsion time of the α -blocker for ureteral stones

	α-blocker Control							Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Agarwal 2009	30.7	19.6	20	39	19.9	20	0.9%	-8.30 [-20.54, 3.94]	
Ates, 2012	4.14	1.78	35	3.61	2.71	44	14.9%	0.53 [-0.46, 1.52]	• •
Cakiroglu 2013	8.34	7.6	59	12.59	8.63	64	8.4%	-4.25 [-7.12, -1.38]	
Cho 2013	9.5	4.8	41	18.6	20.6	43	2.9%	-9.10 [-15.43, -2.77]	
Gravas 2007	12.95	6.92	30	13.22	4.73	31	8.1%	-0.27 [-3.25, 2.71]	+
Janane 2014	8.4	1.8	186	10.6	1.6	170	16.4%	-2.20 [-2.55, -1.85]	•
Kobayashi 2008	15.66	6.14	38	35.47	53.7	34	0.4%	-19.81 [-37.97, -1.65]	
Singh 2011	26.78	11.96	59	31.28	18.31	58	3.5%	-4.50 [-10.11, 1.11]	
Wang 2009	6.1	2.3	34	6.5	2.7	38	14.4%	-0.40 [-1.56, 0.76]	†
Wang 2009	6.2	3	35	6.5	2.7	38	13.9%	-0.30 [-1.61, 1.01]	+
Wang 2010	8.1	1.6	55	11.6	1.4	52	16.1%	-3.50 [-4.07, -2.93]	
Total (95% CI)			592			592	100.0%	-1.90 [-3.09, -0.72]	•
Heterogeneity: Tau ² =	2.20: C	hi ² = 79.	54. df :	= 10 (P -	< 0.000	01); I ² =	87%		
Test for overall effect:	7 = 3.14	(P = 0)	002)						-50 -25 0 25 50
reetter ererun eneet	- 0.14	v - v.	/						Favours [α-blocker] Favours [Control]

The expulsion time of the α -blocker for upper ureteral stones

	α-blocker Control							Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Agarwal 2009	30.7	19.6	20	39	19.9	20	11.9%	-8.30 [-20.54, 3.94]	
Ates, 2012	4.14	1.78	35	3.61	2.71	44	56.2%	0.53 [-0.46, 1.52]	•
Singh 2011	26.78	11.96	59	31.28	18.31	58	31.9%	-4.50 [-10.11, 1.11]	
Total (95% CI)			114			122	100.0%	-2.13 [-6.87, 2.62]	-
Heterogeneity: Tau ² =	: 10.17; (Chi ² = 4	.91, df:	= 2 (P =	0.09); l ^a	²= 59%			-20 -10 0 10 20
Test for overall effect:	Z = 0.88	8 (P = 0.	38)						Favours [α-blocker] Favours [Control]

The expulsion time of the α -blocker for lower ureteral stones

	α-blocker Control							Mean Difference Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	
Gravas 2007	12.95	6.92	30	13.22	4.73	31	18.5%	-0.27 [-3.25, 2.71]		
Wang 2009	6.2	3	35	6.5	2.7	38	26.2%	-0.30 [-1.61, 1.01]		
Wang 2009	6.1	2.3	34	6.5	2.7	38	26.8%	-0.40 [-1.56, 0.76]		
Wang 2010	8.1	1.6	55	11.6	1.4	52	28.5%	-3.50 [-4.07, -2.93]		
Total (95% CI) Heterogeneity: Tau² : Test for overall effect	= 4.04; C : Z = 1.14	hi² = 3 (P = (154 7.49, di).26)	f=3(P	< 0.001	159 001); I ²	100.0 % = 92%	-1.23 [-3.36, 0.89]	-4 -2 0 2 4 Favours [α-blocker] Favours [Control]	

Fig 9. The expulsion time of the α -blocker for ureteral stones.

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experienced retrograde ejaculation, one patient experienced postural hypotension, two patients experienced diarrhea, four patients experienced rhinitis. With regarding to nausea with or without vomiting, four patients experienced in the treatment group, five patients experienced in control group.

The VAS of the α -blocker for renal and ureteral stones

	α-blocker Control							Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Agarwal 2009	2.53	1.79	20	3.83	2.8	20	9.0%	-1.30 [-2.76, 0.16]	
Ates, 2012	6.89	1.02	35	6.59	1.58	44	15.7%	0.30 [-0.28, 0.88]	
Cakiroglu 2013	2.73	2.28	59	3.81	2.74	64	13.2%	-1.08 [-1.97, -0.19]	
Cho 2013	5.33	1.22	41	6.43	1.36	43	15.9%	-1.10 [-1.65, -0.55]	_ - -
Naja 2008	2.867	2.035	51	4.73	2.498	65	13.7%	-1.86 [-2.69, -1.04]	
Singh 2011	2.492	0.757	59	4.181	1.724	58	16.4%	-1.69 [-2.17, -1.21]	_ -
Vicentini 2011	1.57	0.82	38	2.08	1.47	38	16.0%	-0.51 [-1.05, 0.03]	
Total (95% CI)			303			332	100.0%	-1.00 [-1.61, -0.39]	•
Heterogeneity: Tau ² =	: 0.53; C	hi² = 34.	.92, df=	= 6 (P <	0.0000	1); I² = 8	33%		
Test for overall effect:	Z = 3.21	(P = 0.	001)						Favours (α-blocker) Favours (Control)

Proportion of patients with renal or ureteral colic

	α-bloc	ker	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Georgiev 2011	21	99	60	87	44.2%	0.31 [0.21, 0.46]	
Hussein 2010	9	67	21	69	14.3%	0.44 [0.22, 0.89]	
Janane 2014	10	186	40	170	28.9%	0.23 [0.12, 0.44]	
Wang 2008	2	40	8	40	5.5%	0.25 [0.06, 1.11]	
Wang 2010	3	55	10	52	7.1%	0.28 [0.08, 0.97]	
Total (95% CI)		447		418	100.0%	0.30 [0.22, 0.40]	◆
Total events	45		139				
Heterogeneity: Chi ² =	1.89, df=	= 4 (P =	0.76); l ² =	= 0%			
Test for overall effect:	Z=7.94	(P < 0.0	00001)				Favours [α-blocker] Favours [Control]

Fig 10. α -blocker decreasing pain.

PLOS ONE

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The characteristic of this meta-analysis was statistically analyzed the effect of α -blockers on steinstrasse and on different location and size stones.

The shortcoming of this meta-analysis was that there were heterogeneities among studies. The heterogeneities might relate to different duration of treatment, different stone size and location, different ESWL energy and frequency among studies. Most of the included trials failed to describe detail information about randomization and allocation concealment. Lack of blinding procedures in RCTs can also exaggerate the conclusions of these trials. In addition, publication bias should also not be ignored because both the funnel plot and Egger's test showed the possibility of publication bias, even though the Begg's test showed no evidence of publication bias. Further assessment of α -blockers needs to be taken by large-scale clinical studies which employ rigorous methodologies. So the results need to be interpreted cautious-ly. But on the whole, to some extent, the results of this meta-analysis will help clinicians to make some right clinical decisions. As more and more clinical trials take, conclusions will be more credible.

Dizziness

	a-ploc	ker	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Bhagat 2006	1	29	0	29	12.5%	3.00 [0.13, 70.74]	
Cho 2013	2	41	0	43	12.2%	5.24 [0.26, 105.93]	
Janane 2014	5	186	0	170	13.0%	10.06 [0.56, 180.56]	
KÜPELI 2004	1	39	0	39	12.5%	3.00 [0.13, 71.46]	
Park 2013	1	41	0	41	12.5%	3.00 [0.13, 71.56]	
Resim 2005	4	32	0	35	11.9%	9.82 [0.55, 175.48]	
Wang 2008	2	40	0	40	12.5%	5.00 [0.25, 100.97]	
Wang 2010	2	55	0	52	12.8%	4.73 [0.23, 96.30]	
Total (95% CI)		463		449	100.0%	5.48 [1.91, 15.77]	•
Total events	18		0				
Heterogeneity: Chi ² =	0.76, df=	7 (P =	1.00); l ² =	= 0%			
Test for overall effect:	Z = 3.16	(P = 0.0)02)				Favours (α-blocker) Favours [Control]

Headache

	a-blocker Control					Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Moursy 2010	4	44	0	44	20.7%	9.00 [0.50, 162.33]	
Resim 2005	5	32	2	35	79.3%	2.73 [0.57, 13.12]	
Total (95% CI)		76		79	100.0%	4.03 [1.04, 15.72]	
Total events	9		2				
Heterogeneity: Chi² = Test for overall effect:	0.53, df= Z = 2.01 (1 (P = (P = 0.0	0.47); I² =)4)	= 0%			H H

Anejaculation

	a-blocker Control					Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Hussein 2010	5	67	0	69	49.6%	11.32 [0.64, 200.87]	_
Moursy 2010	6	44	0	44	50.4%	13.00 [0.75, 223.98]	
Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	11 0.00, df = Z = 2.42 (111 1 (P = (P = 0.0	0 0.95); I² = 12)	113 = 0%	100.0%	12.17 [1.61, 91.99]	0.01 0.1 1 10 100 Favours [α-blocker] Favours [Control]

Fig 11. Side effects of α -blocker.

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Fig 12. Funnel plot analysis to detect publication bias.

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Supporting Information

S1 PRISMA Checklist. PRISMA checklist. (DOC)

Author Contributions

Conceived and designed the experiments: CPY JHL XLG ZQY. Performed the experiments: MCL TW JY. Analyzed the data: MCL TW SGW. Contributed reagents/materials/analysis tools: MCL TW ZYW. Wrote the paper: MCL ZYW.

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