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Collaborative Review – Stone Disease

Medical Therapy to Facilitate the Passage of Stones: What Is the Evidence?

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Abstract

Context: Medical expulsive therapy (MET) for urolithiasis has gained increasing attention in the last years. It has been suggested that the administration of α-adrenoreceptor antagonists (α-blockers) or calcium channel blockers augments stone expulsion rates and reduces colic events.

Objective: To evaluate the efficacy and safety of MET with α-blockers and calcium channel blockers for upper urinary tract stones with and without prior extracorporeal shock wave lithotripsy (ESWL).

Evidence acquisition: A systematic review of the literature was performed in Medline, Embase, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews searched through 31 December 2008 without time limit. Efficacy and safety end points were evaluated in 47 randomised, controlled trials assessing the role of MET. Meta-analysis was conducted using Review Manager (RevMan) v.5.0 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Evidence synthesis: Pooling of α-blocker and calcium channel blocker studies demonstrated a higher and faster expulsion rate compared to a control group (risk ratio [RR]: 1.45 vs 1.49; 95% confidence interval [CI]: 1.34–1.57 vs 1.33–1.66). Similar results have been obtained after ESWL (RR: 1.29 vs 1.57; 95% CI: 1.16–1.43 vs 1.21–2.04). Additionally, lower analgesic requirements, fewer colic episodes, and fewer hospitalisations were observed within treatment groups.

Conclusions: Pooled analyses suggest that MET with α-blockers or calcium channel blockers augments stone expulsion rates, reduces the time to stone expulsion, and lowers analgesia requirements for ureteral stones with and without ESWL for stones $\leq$10 mm. There is some evidence that a combination of α-blockers and corticosteroids might be more effective than treatment with α-blockers alone. Renal stones after ESWL also seem to profit from MET. The vast majority of randomised studies incorporated into the present systematic review are small, single-centre studies, limiting the strength of our conclusions. Therefore, multicentre, randomised, placebo-controlled trials are needed.

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1. Introduction

The simplest approach to medical expulsion therapy (MET) would be a high fluid intake to increase the hydrostatic pressure proximal to the stone or to increase the volume of urine transported through the ureter, thereby increasing peristaltic activity. The drawback is that it cannot easily be predicted to what extent a ureteral stone obstructs urine flow. In the case of partial or incomplete obstruction, constantly or intermittently, high diuresis is likely to counteract the passage of the stone and cause more pain. A systematic review evaluating the effect of fluids and diuretics found no credible evidence supporting a diuretic approach in terms of pain relief and stone expulsion [1].

An improved understanding of ureteral physiology has led to anti-inflammatory and anti-oedematous treatment with nonsteroidal anti-inflammatory drugs (NSAID) such as nonselective cyclooxygenase (COX) inhibitors or COX-2 inhibitors, decreasing ureteral contractions [2]. However, they appeared not to affect stone expulsion rates in double-blind, placebo-controlled trials [3,4].

Antimuscarinics might relax genitourinary smooth muscle, reducing colic pain [5]. However, a randomised, placebo-controlled trial determining whether N-butylscopolamine (Buscopan) reduces the amount of opioid analgesia required in renal colic demonstrated no favourable effect [6]. Additionally, N-butylscopolamine failed to significantly reduce renal pelvic pressure [7] and was less effective than dipyrone. So far, those regimens have failed to demonstrate an increase in stone expulsion rates.

Phosphodiesterase (PDE) regulates intracellular cyclic nucleotide turnover, influencing smooth muscle tension. Recently, the ureteral smooth muscle relaxing effects of PDE type 4 inhibitor (PDE4-I) and PDE type 5 inhibitor (PDE5-I) in vitro have been reported. Results were similar to those reported for tamsulosin, suggesting the potential for using PDE inhibitors in the treatment of ureteral colic [8,9], but so far, their potential role in expulsion therapy has to be assessed in controlled studies.

Use of corticosteroids with anti-inflammatory action has been reported to facilitate stone expulsion [10]. So far, one randomised trial (published as an abstract) supports a significant effect of methylprednisolone on distal ureteral stone expulsion [11]. However, publications in peer-reviewed journals are necessary. So far, there is no further evidence confirming whether corticosteroids alone are capable of facilitating stone expulsion.

The calcium channel blockers nifedipine and verapamil inhibit endogenous prostaglandin synthesis and calcium influx, reducing spontaneous rhythmic contractions of the human ureter [12]. Similarly, α-blockers inhibit contractions of ureteral musculature, reduce basal tone, and decrease peristaltic frequency and colic pain, possibly facilitating ureteral stone expulsion and suggesting a beneficial effect for MET. This conclusion is further supported by a pilot study investigating the in vivo effect of nifedipine and tamsulosin on ureteral contraction frequency, pressure, and velocity using a ureteric pressure transducer in humans. Both drugs allowed peristalsis to continue, which is important for successful stone expulsion [13]. So far, the most promising drugs studied for MET are α-blockers and calcium channel blockers, mirrored by an increasing study activity and providing the rationale for this systematic review.

2. Evidence acquisition

2.1. Search strategy

The US National Library of Medicine's life science database (Medline), Embase, the Cochrane Central Register of Controlled Trials, and the Cochrane Database for Systematic Reviews were searched through 31 December 2008 without time limit. The Medline search employed a search strategy that included Medical Subject Headings (MeSH) and free-text protocols. The terms *urolithiasis* and *lithotripsy* were used in conjunction with *calcium-channel-blocker, adrenergic alpha-antagonists, prostaglandin antagonists, prostaglandins, cortisone, nifedipine, verapamil, diltiazem, tamsulosin, terazosin, doxazosin, alfuzosin, prazosin, deflazacort, prednisone, medical therapy, drug therapy combination, medical management, expulsive therapy, facilitated passage,* and *adjuvant medical expulsive therapy.*

Reference lists of selected papers and abstracts from the annual meetings of the American Urological Association, European Association of Urology, and the World Congress of Endourology from 2000 to 2008 were hand searched for further eligible studies. Finally, ongoing trials were searched using ClinicalTrials.gov.

2.2. Eligibility criteria for studies incorporated in the final analysis

Studies reporting stone-free rates or time to stone clearance were eligible for incorporation in the final analysis. MET had to be compared to a standard therapy group or a placebo group. Studies consisted of randomised or controlled human trials. After stone expulsion or at the end of the follow-up period, radiologic evaluation was mandatory to confirm stone passage. There was no language restriction for incorporation of studies.

2.3. Quality assessment

The quality of included randomised trials was assessed using the Jadad scale score reporting for each study ranging from 0 to 5 points [14]. Additionally, referring to the Cochrane group, allocation concealment was assessed as adequate (A), unclearly concealed (B), inadequate (C), or not reported (D) [15]. High-quality studies were considered Jadad score >1 plus allocation concealment A or Jadad ≥ 3 plus allocation concealment B, C, or D.

2.4. Statistical analysis

Statistical analysis was performed using Review Manager (RevMan) v.5.0 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). A p value <0.05 was

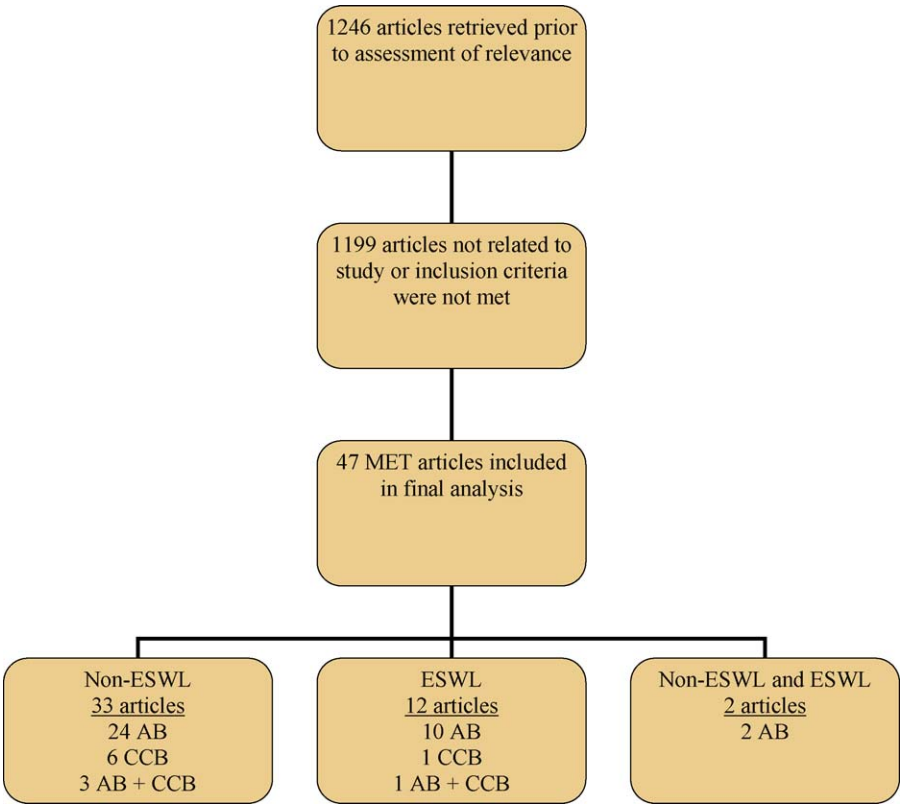


Fig. 1 – Forty-seven articles were identified, including 12 abstracts and 1 completed, unpublished trial, of which 14 studies were classified as high quality, with a Jadad score ≥3. MET = medical expulsive therapy; ESWL = extracorporeal shock wave lithotripsy; AB = α-blocker; CCB = calcium channel blocker.

considered statistically significant. Mantel-Haenszel test pooled risk ratios (RRs) and 95% confidence intervals (CIs) were calculated for the effects of α-blockade and calcium channel blockers in patients undergoing MET with and without prior extracorporeal shock wave lithotripsy (ESWL). The χ^2 test was used to detect statistical heterogeneity. Fixed-effects models were applied in the absence of heterogeneity, whereas random-effects models were applied when heterogeneity was present, providing a more conservative estimate with a wider CI [16]. A p value <0.1 suggests significant heterogeneity, meaning that the difference in results among the individual studies is not likely to have been caused by chance.

To quantify statistical heterogeneity across studies, the I^2 statistic was used. The I^2 statistic describes the percentage of variation across studies that is the result of heterogeneity rather than chance. An I^2 >50% suggests substantial heterogeneity. Inverted funnel plots assessed the presence of publication bias. The RR for stone expulsion was plotted against the standard error (SE) of the log(RR). Forest plots were applied demonstrating RR in each square with the area proportional to the number of events; 95% CIs are visible as horizontal lines. Overall RR and corresponding 95% CIs are plotted as a diamond. Squares and diamonds to the right of the vertical line of no effect indicate a treatment benefit. This benefit is significant ($p < 0.05$) only if the horizontal line or diamond does not overlap the vertical line.

Absolute risk reduction (ARR) demonstrated a decrease in risk of the treatment group in relation to the control group. It is calculated as the arithmetic difference of the number of events in treated or control groups divided by the number of people in that group. Withdrawals, dropouts, and patients lost to follow-up were considered as participants in an intention-to-treat analysis protocol.

The sections that follow refer to the search results shown in Fig. 1.

3. Evidence synthesis

3.1. Quality assessment of studies incorporated in the final analysis

Jadad scores ranged from 0 to 5, with a median score of 2. Five double-blind studies were reported (Table 1). Allocation concealment was rarely assessable (level A was applicable to only one trial [17]) and therefore could not be integrated into the quality assessment.

3.2. Quantitative analysis for medical expulsive therapy without shock wave lithotripsy

3.2.1. α-Blocker therapy

Twenty-nine studies [17–45] were analysed, including 2419 patients (Fig. 2). Funnel plot analysis suggested the

Table 1 – Efficacy and safety data from the randomised controlled trials at different formulations for medical expulsive therapy

Author, yr	Jadad score	Double blinded	Power calc.	Standard therapy	Treatment + standard therapy vs control	Expulsion rate:sample size (%)	Expulsion time, d	Stone size Mean[¥] median	Stone location Size range	Adverse events, minor; severe		Drop-outs (%)
Autorino, 2005 [25]	3	No	Yes	Diclofenac 100 mg, aescin 80 mg, omeprazol 20 mg, levofloxacin 250 mg	Tamsulosin Control	28:32 (88) 19:32 (59)	4.8 ± 2.2 7.4 ± 2.2	6.5[¥] 5.7	Distal ureter 3–10 mm	6%; 6%	Dizziness, trans-hypotension	0 (0)
Avdoshin, 2005 [26]	2	No	–	Anticholinergic	Tamsulosin Control	31:42 (74) 11:45 (24)	–	7.4[¥] 7.4	–	–	–	–
Ayubov, 2007* [36]	1	No	–	Diclofenac 75 mg	Doxazosin Control	28:30 (93) 19:31 (61)	5.4 8.4	–	Distal ureter –	–	–	–
Borghi, 1994 [46]	4	Yes	–	Methylprednisolone 16 mg	Nifedipine	34:43 (79)	11.2	6.4[¥]	Ureter	9.3%; 14% $p < 0.05$	Headache, premalleolar oedema, stomach ache	9 (14)
					Placebo	24:43 (56)	16.4	5.3	4–15 mm		Decrease systolic + diastolic blood pressure, increase in heart rate	
Cervenakov, 2002 [19]	3	Yes	–	Tramal 50 mg, diazepam 5 mg, yellon 120 mg, veral 150 mg	Tamsulosin Control	41:51 (80) 32:53 (60)	3.1 3.4	–	Distal ureter ≤10 mm	–	–	0 (4)
Cooper, 2000 [47]	2	No	–	Ketorolac 40 mg, oxycodone, acetaminophen, prochlorperazine	Nifedipine XL 30 mg, prednisone 20 mg, trimethoprim/sulfa	31:35 (86) 19:35 (54)	12.6 11.2	3.9[¥] 3.9	Ureter 2–6 mm	54.3%; 40%	Vomiting, nausea, dyspepsia, drowsiness	4
Dellabella, 2003 [20]	2	No	–	Deflazacort 30 mg, cotrimoxazole 640 mg, diclofenac 75 mg on demand	Tamsulosin Floroglucine-trimetossibenzene	30:30 (100) 21:30 (70)	2.7 4.6	6.7[¥] 5.8	Juxtavesical 4–13 mm	0	0	0 (0)
Dellabella, 2005 [28]	3	No	Yes	Deflazacort 30 mg, cotrimoxazole 640 mg, diclofenac 75 mg on demand	Tamsulosin Nifedipine Phloroglucinol	68:70 (97) 54:70 (77) 45:70 (64)	3 5 5	7.2[¥] 6.2 6.2	Distal ureter >4 mm	–	–	–
De Sio, 2006 [29]	3	No	–	Diclofenac 100 mg, aescin 80 mg, omeprazol 20 mg, levofloxacin 250 mg	Tamsulosin Control	45:50 (90) 27:46 (59)	4.4 ± 2.1 7.5 ± 1.8	6.9[¥] 6.4	Juxtavesical ≤10 mm	4.3%; 6% $p = 0.05$	Dizziness, hypotension	0 (0)
Erturhan, 2007 [35]	1	No	–	Cefuroxime 250 mg, diclofenac max. 200 mg on demand	Tamsulosin	43:60 (72)	7	7[¥]	Distal ureter	3.3%; 0%; 6.7%; 6.7%	–	2 (7)
					Tamsulosin + tolterodine 4 mg Tolterodine 4 mg Control	26:60 (43)	11.8	7	<10 mm			
Han, 2006 [33]	2	No	–	Caroverine 20 mg, ketorolac 30 mg on demand	Tamsulosin 0.2 mg Control	29:35 (83) 17:32 (53)	4.6 8.3	4.4[¥] 4.3	Distal ureter	–	–	–
Hong, 2008* [42]	1	No	–	Furosemide 40 mg	Tamsulosin Tamsulosin + deflazacort 24 mg	119:138(86) 27:42 (64)	–	5.1[¥] 4.9	Distal ureter <10 mm	No SAE	–	–

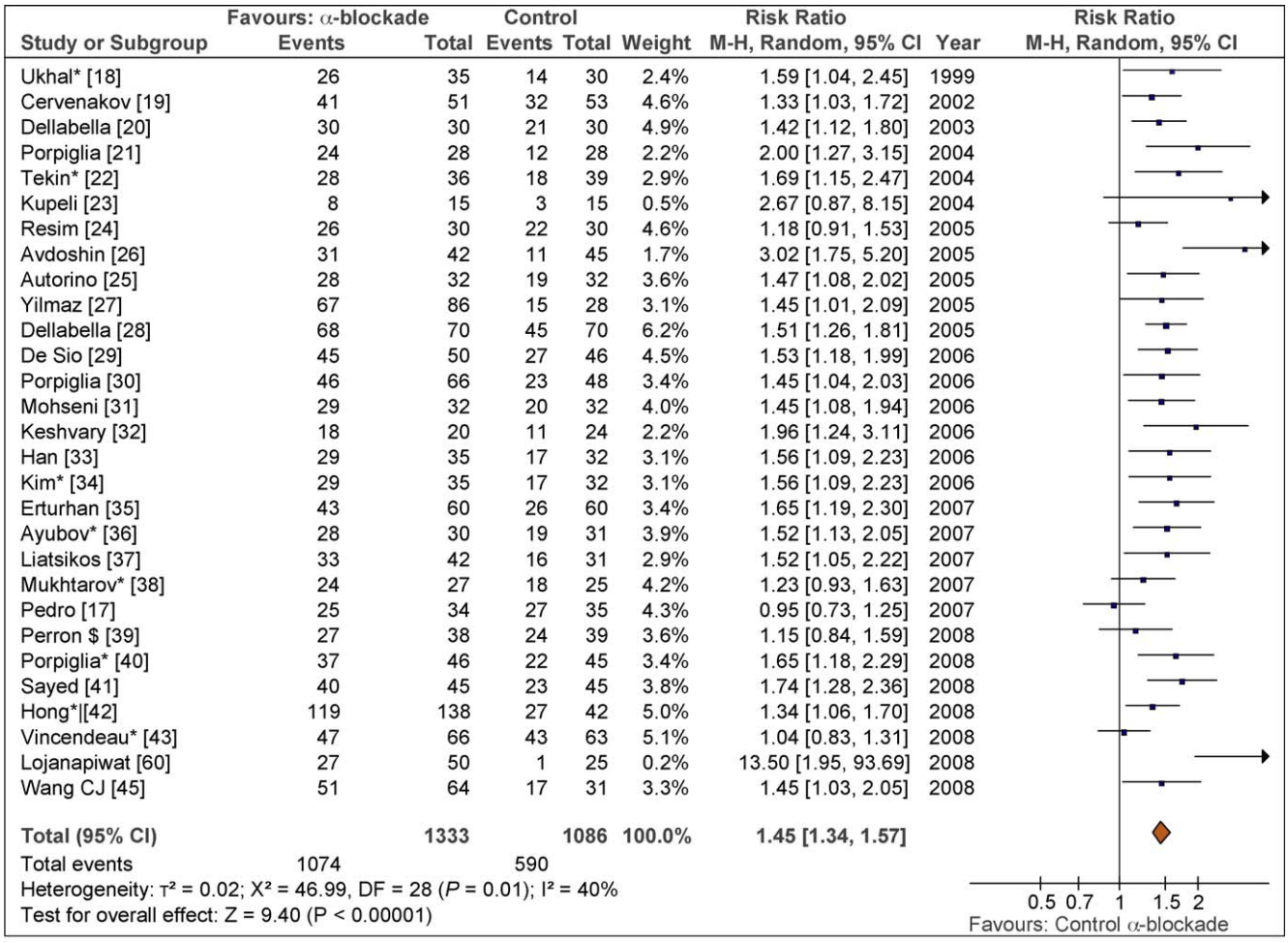
Keshvary, 2006 [32]	1	No	–	None	Tamsulosin	18:20 (90)	8.2	6.7¥	Juxtavesical	–	–	–
					Nifedipine 20 mg	14:20 (75)	20	6.4	<10 mm			
					Placebo	11:24 (46)	14.2	6.8				
Kim, 2006* [34]	1	No	–	Ketorolac 30 mg on demand	Tamsulosin 0.2 mg	29:35(83)	4.6	4.4¥	Distal ureter	–	–	–
					Caroverine 60 mg	17:32(53)	8.3	4.3	<5 mm			
Küpeli, 2004 [23]	3	No	–	Diclofenac 100 mg	Tamsulosin≤5 mm	8:15 (53)	–	4.7¥	Distal 5 cm	2.5%	Dizziness	–
					Control ≤5 mm	3:15 (20)		4.9	3–15 mm			
Liatsikos, 2007 [37]	2	No	Yes	Diclofenac 75 mg on demand	Doxazosin <5 mm	17:20 (85)	7.6 ± 0.8	3.2¥	Distal ureter	0	0	–
					Control <5 mm	9:15 (60)	8.8 ± 1.09	3	≤10 mm			
					Doxazosin >5 mm	16:22 (73)	7.1 ± 1.29	7.8				
					Control >5 mm	7:16 (44)	12.1 ± 1.35	7.7				
Lojanapiwat, 2008 [60]	2	No	–	Diclofenac 100 mg	Tamsulosin 0.2 mg	10:25 (40)	9.3 ± 6.06	6.4¥	Distal ureter	0	0	0 (0)
					Tamsulosin 0.4 mg	17:25 (68)	10.8 ± 7.52	6.3	4–10 mm			
					Control	1:25 (4)	23 ± 0	6.7				
Mohseni, 2006 [31]	2	No	–	Indomethacin, pethidine on demand	Terazosin	32:29 (91)	3.2 ± 2.59	6.9	Distal ureter	–	–	–
					Control	32:20 (63)	5.9 ± 2.7	6.6	–			
Mukhtarov, 2007 [38]	1	No	–	Diclofenac on demand	Doxazosin <6 mm	24:27 (89)	6.4	4.1¥	Distal ureter	–	–	–
					Control <6 mm	18:25 (72)	8.8	4.1	2–15 mm			
Pedro, 2007 [17]	5	Yes	Yes	None	Alfuzosin	34:25 (74)	5.2 ± 4.82	3.8¥	Distal ureter	12%; 0	Dizziness, hypotension	13
					Placebo	35:27 (77)	8.5 ± 6.99	4.1	<8 mm			
Perron [39], completed 2008	3	No	Yes	Ibuprofen 2.4 g, oxycodone 20–60 mg	Tamsulosin	27:40 (77)	1	3.5¥	Distal ureter	0	0	1
					Control	24:40 (65)	2	3.8				
Porpiglia, 2000 [49]	3	No	–	Diclofenac 75 mg on demand	Nifedipine SR + deflazacort 30 mg	38:48 (79)	7	5.8¥	Distal ureter	4.2%, 21%	Hypotension, palpitations, headache, asthenia	4 (4)
					Control	17:48 (35)	20	5.5	≤10 mm			
Porpiglia, 2004 [21]	3	No	–	Diclofenac 75 mg on demand	Tamsulosin + deflazacort 30 mg, Nifedipine SR + deflazacort 30 mg	24:28 (85)	7.9	5.4¥	Juxtavesical	14.3%; 13.3%	–	1
					Control	24:30 (80)	9.3	4.7	<10 mm			
						12:28 (43)	12	5.4				
Porpiglia, 2006 [30]	2	No	Yes	Diclofenac 75 mg on demand	Tamsulosin	18:30 (60)	7	5.9¥	Juxtavesical	6.1%; 0	Hypotension	3
					Deflazacort 30 mg	9:24 (38)		5.7	≥5 mm			
					Tamsulosin + deflazacort	28:33 (85)						
					Control	8:24 (33)						
Porpiglia, 2008* [40]	1	No	–	Diclofenac 100 mg on demand	Tamsulosin	37:46 (80)	1	5.9¥	Distal ureter	0	0	–
					Control	22:45 (49)	5	6.3	>5 mm			
Resim, 2005 [24]	2	No	–	Tenoxicam 20 mg	Tamsulosin	26:30 (87)	6	7.8¥	Juxtavesical	36.7%; 40%	Headache, dizziness, diarrhoea, retrograde ejaculation	0 (0)
					Control	22:30 (73)		7.8	5–13 mm			
Saita, 2004 [50]	1	No	–	Prednisolone 25 mg, NSAIDs on demand	Nifedipine SR	15:25 (60)	6	12¥	Ureter	24%; 28%	Erythema, stomach ache, pain	10 (15)
					Control	12:25 (48)	10	12.8	≤15 mm			

Table 1 (*Continued*)

Author, yr	Jadad score	Double blinded	Power calc.	Standard therapy	Treatment + standard therapy vs control	Expulsion rate:sample size (%)	Expulsion time, d	Stone size Mean[¥] median	Stone location Size range	Adverse events, minor; severe		Drop-outs (%)
Sayed, 2008 [41]	2	No	–	Diclofenac 100 mg on demand, levofloxacin 250 mg	Tamsulosin	40:45 (90)	7.3 ± 0.78	6.8[¥]	Distal ureter	No SAE	–	0 (0)
					Control	23:45 (51)	12.5 ± 2.12	6.4				
Skrekas, 2003* [51]	1	No	–	Nimesulide 200 mg	Nifedipine	38:46 (83)	6	5[¥]	Distal ureter	–	–	–
					Control	26:46 (57)	18	5.5	<10 mm			
Staerman, 2000* [48]	1	No	–	Ketoprofene 200 mg, phloroglucinol 500 mg	Nifedipine	21:23 (91)	5.1	4.5[¥]	Distal ureter	–	–	–
					Control	16:25 (64)	12.9	4.3	–			
Tekin, 2004* [22]	1	No	–	No active treatment	Terazosin	28:36 (78)	–	7.3[¥]	Distal ureter	–	–	0 (0)
					Control	18:39 (46)		6.8	<15 mm			
Ukhal, 1999* [18]	1	No	–	Analgesics, spasmolytics, sedatives, phytoextracts	Doxazosin 2 mg	26:35 (74)	–	7.1[¥]	Distal ureter	–	–	–
					Control	14:30 (47)		7.1	5–9 mm			
Vincendeau, 2008* [43]	4	Yes	–	Placebo	Tamsulosin	47:66 (71)	9.6 ± 9.8	2.9[¥]	Distal ureter	N/A	–	8 (3)
						43:63 (68)	10.1 ± 10	3.2	2–7 mm			
Wang, 2008 [45]	3	No	–	Ketorolac 30 mg, buprenorphine 0.2 mg on demand	Tamsulosin	26:32 (81)	6.3 ± 2.4	6.5[¥]	Distal ureter	3.1%; 15.6%	Hypotension, asthenia, syncope, palpitations	0 (0)
					Terazosin 0.2 mg	25:32 (78)	6.3 ± 2.1	6.5	<10 mm			
					Control	17:31 (55)	10.1 ± 3	6.5				
Yilmaz, 2005 [27]	3	No	–	Diclofenac 75 mg on demand	Doxazosin	22:29 (76)	5.9 ± 0.59	5.9[¥]	Juxtavesical	No SAE	–	0 (0)
					Tamsulosin	23:29 (79)	6.3 ± 0.88	6	≤10 mm			
					Terazosin	22:28 (79)	5.8 ± 0.88	6				
					Control	15:28 (54)	10.5 ± 2.12	6.1				
Bhagat, 2007 [54] SWL	3	Yes	–	Proxyvon, diclofenac + pethidine on demand	Tamsulosin	28:30 (93)	–	–	Kidney 6–24 mm	3.4%; –	Dizziness	3 (3)
					Placebo	23:30 (77)			Ureter 6–15 mm			
Gravas, 2007 [55] SWL	2	No	Yes	Diclofenac 50 mg on demand	Tamsulosin	20:30 (67)	13	8.5[¥]	Ureter	6.7%; 0%	Dizziness	3 (6)
					Control	18:31 (52)	13.2	8.3	≥6 mm			
Gravina, 2005 [52] SWL	3	No	Yes	Methylprednisolone 32 mg, diclofenac 75 mg on demand	Tamsulosin	51:65 (79)	–	14.2[¥]	Kidney	No SAE	–	13
					Control	39:65 (60)		14.6	4–20 mm			
Han, 2006 [33] SWL	1	No	–	Caroverine 20 mg, ketorolac 30 mg on demand	Tamsulosin 0.2 mg	20:22 (91)	8.2	8.2[¥]	Upper ureter	–	–	–
					Control	15:23 (65)	7.9	7.9	6–12 mm			
Kobayashi, 2008 [57] SWL	1	No	–	None	Tamsulosin 0.2 mg, coreito 7.5 g	32:38 (84)	15.7 ± 614	10.6[¥]	Ureter	–	–	–
					Control	30:34 (88)	35.5 ± 53.7	9.9	>4 mm			
Küpeli, 2004 [23] >5 mm SWL	3	No	–	Diclofenac 100 mg	Tamsulosin >5 mm	17:24 (71)	–	8.6[¥]	Distal 5 cm	0	Dizziness	–
					Control >5 mm	8:24 (33)		8.2	3–15 mm			
Lee, 2008* [58] SWL	1	No	–	Trospium chloride	Alfuzosin	30:31(97)	16.4 ± 7.5	–	Distal ureter	–	–	–
					Tamsulosin 0.2 mg	40:43(93)	17.6 ± 8.44		>5 mm			
					Control	20:34(59)	25.5 ± 96.5					

Micali, 2007 [53] SWL	0	No	–	Diclofenac 75 mg on demand, ketoprofene 100 mg for 7 d	Nifedipine upper ureter Control upper ureter Tamsulosin distal ureter Control distal ureter	30:35 (86) 15:29 (52) 23:28 (82) 12:21 (57)	–	10.4¥ 10.3 10 9.9	Upper ureter 7–14 mm Distal ureter 7–13 mm	No SAE	–	–
Mukhtarov, 2007 [38] >6 mm SWL	1	No	–	Diclofenac on demand	Doxazosin >6 mm Control >6 mm	24:24 (100) 17:21(81)	8 13.5	8.9¥ 8.9	Distal ureter 6–15 mm	–	–	–
Naja, 2008 [59] SWL	3	No	Yes	None	Tamsulosin Control	27:67 (40)¥ 20:72 (28)¥	–	12.1¥ 13	Renal pelvis, superior + middle cal. 6–20 mm	2%;2%	Hypotension, retrograde ejaculation	24 (10)
Porpiglia, 2002 [62] SWL	2	No	–	Diclofenac 75 mg on demand	Nifedipine SR + deflazacort 30 mg Control	30:40 (75) 20:40 (50)	–	11.6¥ 10.1	Upper/lower ureter	10%; 0%	Asthenia, headache	0 (0)
Resim, 2005 [24] SWL	2	No	–	Tenoxicam 20 mg	Tamsulosin Control	24:32 (75) 23:35 (66)	9 10	21 20	Ureter Steinstrasse	40.6%; 20%	Headache, dizziness, diarrhoea, retrograde ejaculation, nausea	–
Shaaban, 2008* [56] SWL	1	No	–	Diclofenac on demand	Doxazosin Control	48:52 (92) 40:53 (75)	7 14	–	Upper tract 5–20 mm	15%;0%	–	–
Wang, 2008* [69] SWL	1	No	–	None	Tamsulosin Control	31:40 (78) 18:40 (45)	–	–	Distal ureter –	5%; 0%	Dizziness	–

SR = sustained release; NSAID = nonsteroidal anti-inflammatory drug; N/A = not applicable; SWL = shock wave lithotripsy.
*: As abstract available only.
¥: Mean stone size.
When not indicated, alternatively tamsulosin 0.4 mg was administered.



* Abstract
$ Study completed in 2008.

Fig. 2 – Forest plot of comparison: α-blockade versus control. M-H = Mantel-Haenszel; CI = confidence interval; DF = degree of freedom.

presence of a mild publication bias (Fig. 3). Moderate heterogeneity was detected ($P = 0.01$; $I^2 = 40\%$). Pooling demonstrated an overall benefit for stone expulsion (RR: 1.45; 95% CI: 1.34–1.57). After excluding eight studies in which patients received medications other than diclofenac or ketolorac, only minor changes occurred ($I^2 = 43\%$; RR: 1.45; 95% CI: 1.31–1.59). Only one study reported a RR of <1 (RR: 0.95; 95% CI: 0.73–1.25), denoting an event reduction in the α-blocker group [17]. Overall, pooling resulted in an ARR of 0.27.

3.2.1.1. Tamsulosin 0.4 mg versus control. After including 10 high-quality studies with a Jadad score ≥3, the presence of heterogeneity was markedly reduced ($P = 0.16$; $I^2 = 31\%$; Fig. 4). Pooling of 816 patients demonstrated an overall benefit for stone expulsion (RR: 1.40; 95% CI: 1.28–1.54) and an ARR of 0.24.

3.2.1.2. Tamsulosin 0.2 mg versus control. Four Asian studies investigated tamsulosin 0.2 mg versus a control group including 247 patients (Fig. 5). No significant heterogeneity was detected ($P = 0.24$; $I^2 = 28\%$). Pooling demonstrated an overall benefit for stone expulsion (RR: 1.56; 95% CI: 1.21–2.03) and an ARR of 0.28.

3.2.1.3. Doxazosin versus control. Five studies investigated doxazosin versus a control group including 308 patients (Fig. 6). Heterogeneity was not observed ($P = 0.8$; $I^2 = 0\%$) Pooling demonstrated an overall benefit for stone expulsion (RR: 1.45; 95% CI: 1.24–1.70) and an ARR of 0.25.

3.2.1.4. Terazosin versus control. Three studies investigated terazosin versus a control group including 241 patients (Fig. 7). Heterogeneity was not observed ($P = 0.9$; $I^2 = 0\%$). Pooling demonstrated an overall benefit for stone expulsion (RR: 1.45; 95% CI: 1.18–1.77) and an ARR of 0.26.

3.2.1.5. Alfuzosin versus control. Only one study compared the outcome of alfuzosin versus a control group for distal ureteral stones in a placebo-controlled, double-blind fashion. No increase of the spontaneous expulsion rate was found in the alfuzosin group (77.1% vs 73.5%, $p = 0.83$), although patients

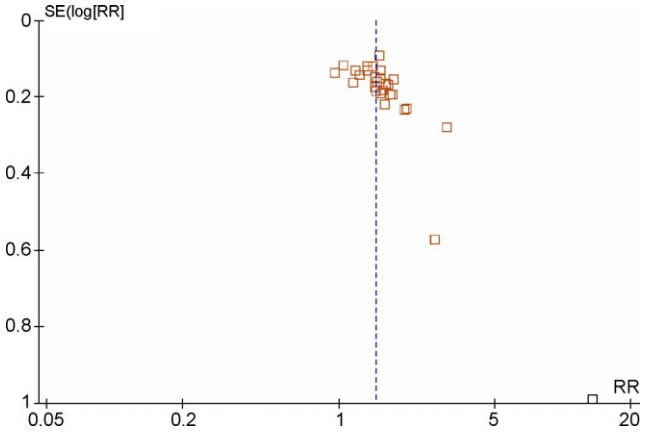


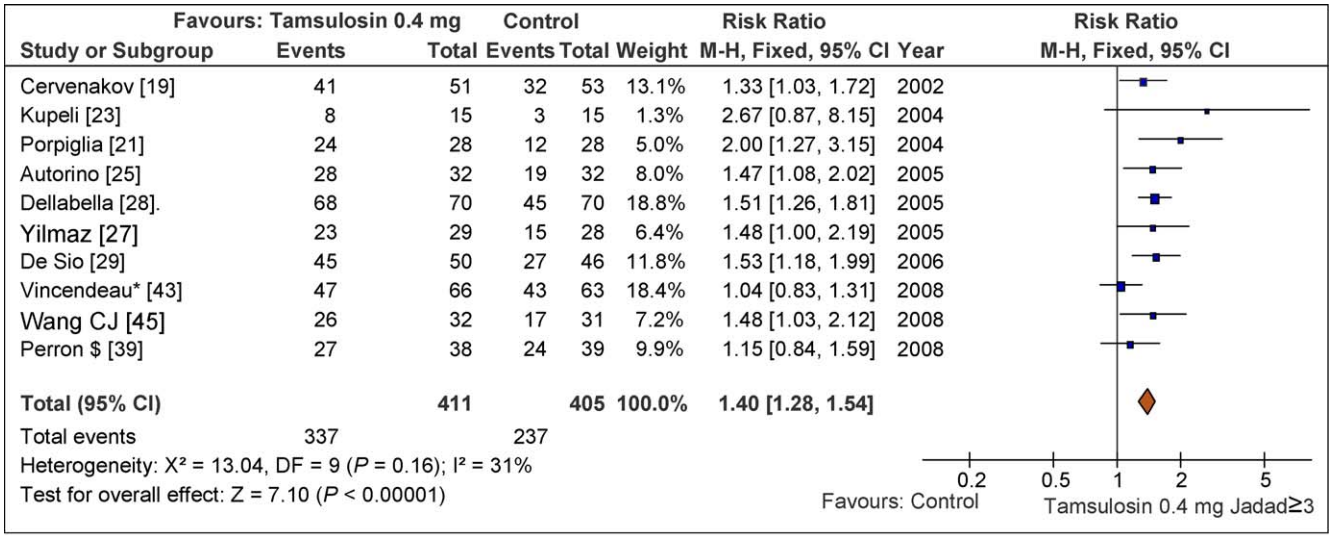
Fig. 3 – α-Blockade funnel plot: Clusters around the overall estimated treatment effect at midline suggest a mild publication bias. SE = standard error; RR = risk ratio.

reported improved comfort and a decreased time to stone expulsion in the treatment group of 5.2 ± 4.82 d versus 8.5 ± 6.99 d in the control group ($p = 0.003$).

3.2.2. *Calcium channel blocker therapy*

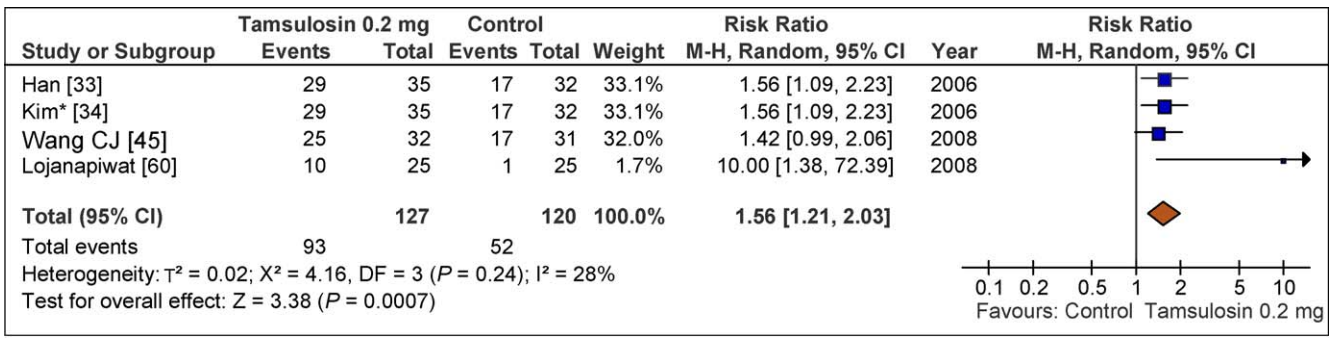
All nine studies investigating calcium channel blockers used nifedipine for medical stone expulsion therapy (Fig. 8) [21,28,32,46–51]. Overall, 686 patients were included. Pooling demonstrated a higher stone expulsion rate (RR: 1.49; 95% CI: 1.33–1.66). No study denoted an event reduction in the nifedipine group. Heterogeneity was minimal ($P = 0.27$; $I^2 = 19\%$). Funnel plot analysis did not suggest a significant publication bias (Fig. 9). An ARR of 0.26 was observed.

Seven studies included patients with distal ureteral/juxtavesical stones only, and two studies included middle and upper ureteral stones, as well. Six of the nine studies reported a decreased time to stone expulsion between 2.7 and 12 d in favour of the nifedipine group (Table 1).



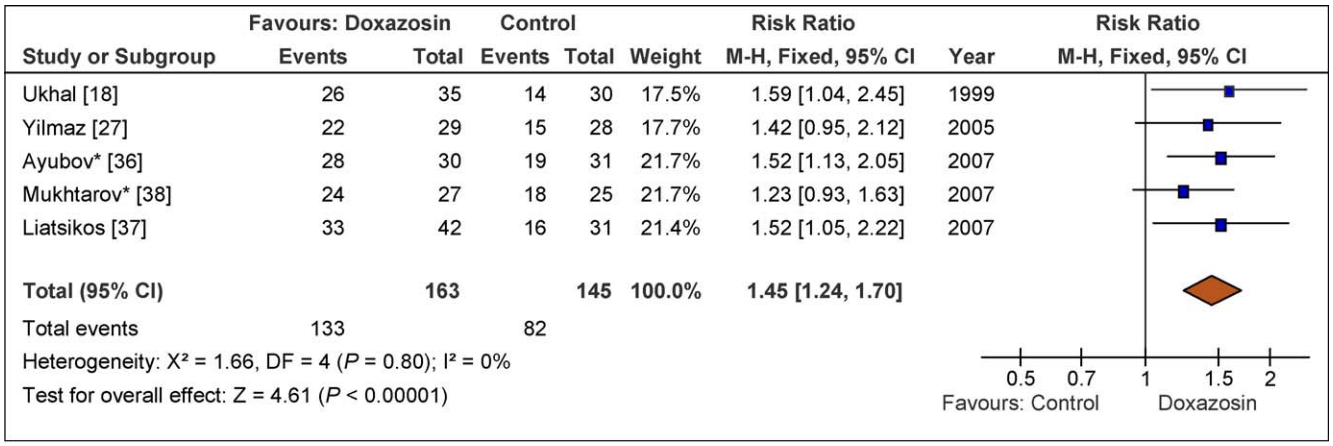
* Abstract
$ Study completed in 2008.

Fig. 4 – Forest plot of comparison: control versus tamsulosin 0.4 mg, Jadad score ≥3. M-H = Mantel-Haenszel; CI = confidence interval; DF = degree of freedom.



* Abstract

Fig. 5 – Forest plot of comparison: control versus tamsulosin 0.2 mg. M-H = Mantel-Haenszel; CI = confidence interval; DF = degree of freedom.



* Abstract

Fig. 6 – Forest plot of comparison: control versus doxazosin. M-H = Mantel-Haenszel; CI = confidence interval; DF = degree of freedom.

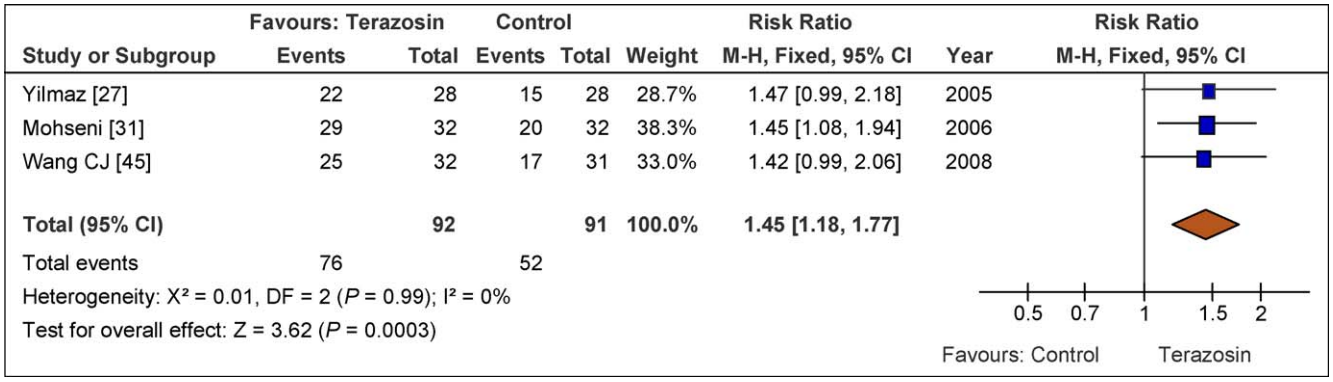


Fig. 7 – Forest plot of comparison: control versus terazosin. M-H = Mantel-Haenszel; CI = confidence interval; DF = degree of freedom.

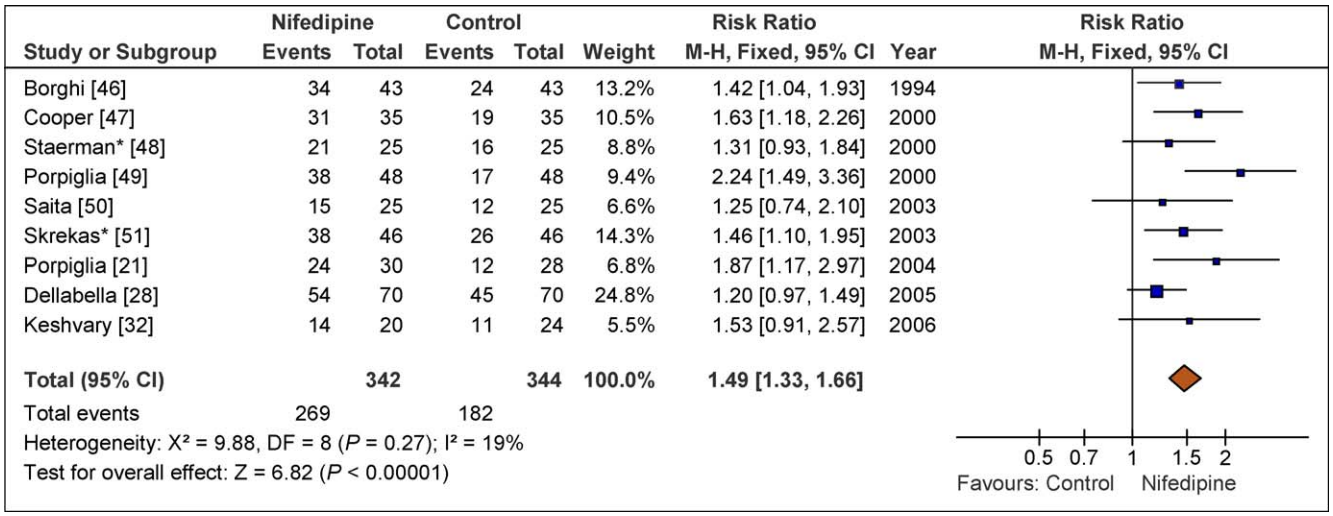


Fig. 8 – Forest plot of comparison: control versus nifedipine. M-H = Mantel-Haenszel; CI = confidence interval; DF = degree of freedom.

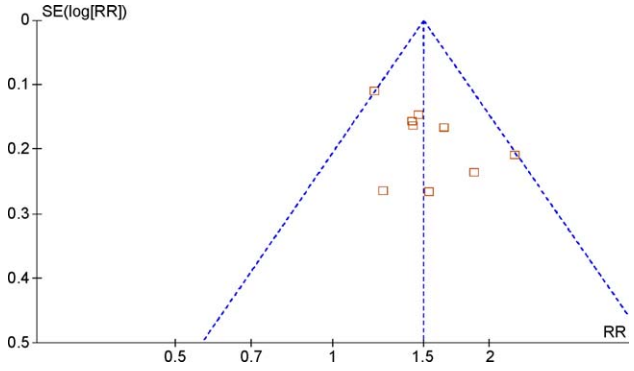


Fig. 9 – Nifedipine funnel plot: Even distribution around the overall treatment effect within the pseudo-95% confidence interval limits for estimated treatment effects suggests a mild publication bias. SE = standard error; RR = risk ratio.

3.3. *Quantitative analysis for medical expulsive therapy with shock wave lithotripsy*

3.3.1. *Shock wave lithotripsy plus α-blocker therapy*

Overall, 13 studies were analysed, including 1007 patients (Fig. 10) [23,24,33,38,52–60]. One study used alfuzosin and tamsulosin [58]; 10 studies used tamsulosin only [23,24,33,52–55,57,59,60], of which 3 Asian studies used the 0.2-mg formulation [33,57,58]; and two studies used doxazosin [38,56]. Pooling demonstrated an overall benefit for stone expulsion (RR: 1.29; 95% CI: 1.16–1.43). Only one study, using tamsulosin 0.2 mg [57], reported a RR of <1, denoting an event reduction in the α-blocker group. Moderate heterogeneity was detected, analysing all studies using α-blocker compared to a standard therapy ($P = 0.05$; $I^2 = 44\%$). Funnel plot analysis suggested the presence of a mild publication bias. Overall, an ARR of 0.21 was detected. Of 10 studies assessing the time to stone expulsion, 9 reported a decrease after α-blocker treatment (Table 1).

3.3.2. *Shock wave lithotripsy plus tamsulosin 0.4 mg versus control*

After pooling three high-quality studies with Jadad ≥3, no heterogeneity was detected ($P = 0.68$; $I^2 = 0\%$; RR: 1.32; 95% CI: 1.11–1.56). Only minor changes were observed with all seven trials using tamsulosin 0.4 mg, irrespective of the reported Jadad score, including 552 patients ($P = 0.46$; $I^2 = 0\%$; RR: 1.38; 95% CI: 1.22–1.56) with an ARR of 0.2.

3.3.3. *Shock wave lithotripsy plus doxazosin versus control*

Two trials including 150 patients investigated the treatment effect of doxazosin after ESWL versus a control. Both studies demonstrated an effect in favour of the treatment group. No heterogeneity was detected ($P = 0.96$; $I^2 = 0\%$; RR: 1.23; 95% CI: 1.07–1.41) with an ARR of 0.18.

3.3.4. *Shock wave lithotripsy plus alfuzosin versus control*

One study compared the outcome of ESWL plus alfuzosin versus a standard therapy group receiving trospium chloride for distal ureteral stones >5 mm [58]. The expulsion rate and time to stone expulsion were in favour of the treatment group ($p < 0.05$).

3.3.5. *Shock wave lithotripsy and calcium channel blocker therapy (nifedipine)*

Two studies [53,61] including 144 patients demonstrated an overall treatment benefit for stone expulsion (RR: 1.57;

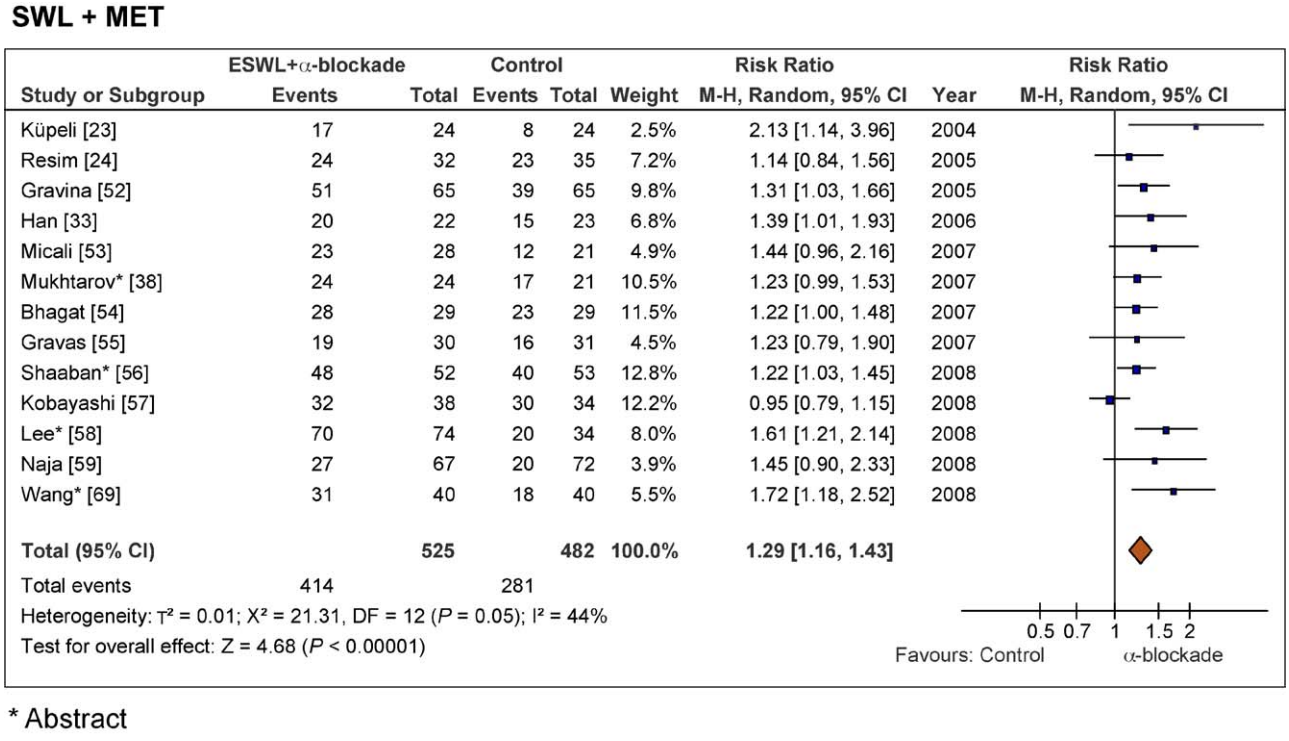


Fig. 10 – Forest plot of comparison: control versus α-blockade following extracorporeal shock wave lithotripsy. ESWL = extracorporeal shock wave lithotripsy; M-H = Mantel-Haenszel; CI = confidence interval; DF = degree of freedom.

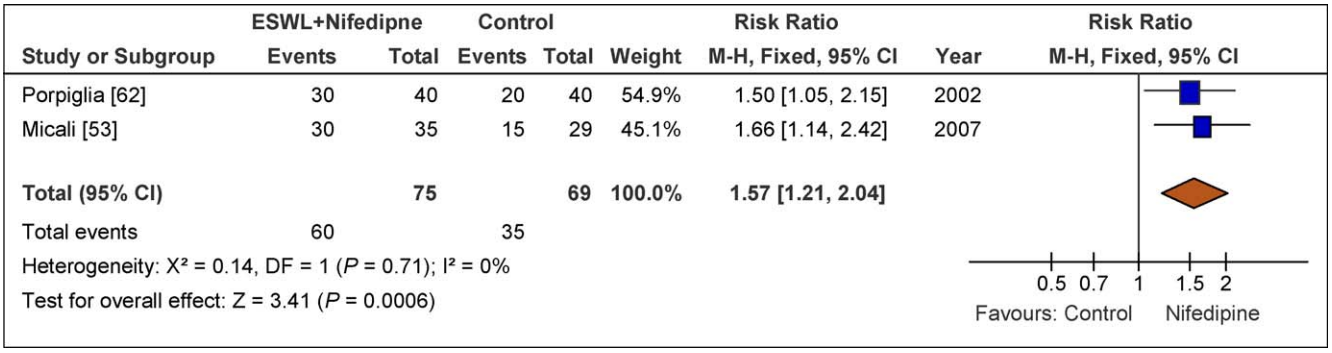


Fig. 11 – Forest plot of comparison: control versus nifedipine after extracorporeal shock wave lithotripsy. ESWL = extracorporeal shock wave lithotripsy; M-H = Mantel-Haenszel; CI = confidence interval; DF = degree of freedom.

95% CI: 1.21–2.04; Fig. 11). No heterogeneity was detected ($P = 0.71$; $I^2 = 0\%$) with an ARR of 0.3.

3.4. *Quantitative analysis for stone size and medical expulsive therapy*

Stone sizes in both α-blocker and nifedipine groups ranged from 2 to 15 mm (Table 1).

3.4.1. *α-Blocker (stone size <5 mm vs ≥5 mm)*

Pooling nine trials including 585 patients with a mean stone size <5 mm using tamsulosin detected mild heterogeneity ($P = 0.14$; $I^2 = 35\%$; RR: 1.25; 95% CI: 1.12–1.40) with an ARR of 0.15. Pooling 20 trials including 1740 patients with a mean stone size ≥5 mm using tamsulosin detected mild heterogeneity ($P = 0.31$; $I^2 = 12\%$; RR: 1.62; 95% CI: 1.50–1.74) with an ARR of 0.31.

3.4.2. *Nifedipine (stone size <5 mm vs ≥5 mm)*

Pooling two trials including 120 patients with a mean stone size <5 mm detected no heterogeneity ($P = 0.36$; $I^2 = 0\%$; RR: 1.49; 95% CI: 1.17–1.88) with an ARR of 0.28. Pooling seven trials including 566 patients with a mean stone size ≥5 mm detected mild heterogeneity ($P = 0.17$; $I^2 = 34\%$; RR: 1.49; 95% CI: 1.31–1.69) with an ARR of 0.25.

3.5. *Adverse events*

A substantial number of studies (>45%) reported neither adverse events nor drop-out rates (Tables 2 and 3). The same applies for the number of colic episodes, the amount of analgesia required, hospitalisation rates, and the number of work days lost.

Variations of reported adverse events and drop-out rates have been reported for both nifedipine and tamsulosin. Studies excluding hypotensive patients reported drop-outs resulting from hypotension or palpitations in 3.3–4.2% of patients [46,49], whereas other studies investigating nifedipine observed neither drop-outs [49,53] nor increased adverse events compared to placebo [46,50].

After administration of tamsulosin, the most frequently reported adverse event was transient hypotension [25,41,54,62]. No difference in adverse events was noted between tamsulosin 0.4 mg and 0.2 mg [63]. Of 16 studies reporting drop-out rates, only 3 demonstrated a higher drop-out rate in the tamsulosin group compared to control [21,43,59]. Data reporting adverse events for alfuzosin, doxazosin, and terazosin were sparse. However, Pedro et al

Table 2 – Differences in analgesic requirements, colic episodes, and hospitalisation rates between treatment groups and controls

	α-Blocker	Control	*p* value
Analgesic requirements			
Autorino, 2005 [25]			0.003
Ayubov, 2007 [36]			<0.0001
Dellabella, 2003 [20]			<0.0001
Dellabella, 2005 [28]			<0.0001
De Sio, 2006 [29]			0.003
Erturhan, 2007 [35]			n.s.
Han, 2006 [33]			0.04
Kim, 2006 [34]			<0.0001
Mohseni, 2006 [31]	Analgesic		0.04
Pedro, 2007 [17]	requirements		n.s.
Porpiglia, 2004 [21]	were lower for		<0.0001
Porpiglia, 2006 [30]	all α-blocker		<0.001
Porpiglia, 2008 [40]	studies compared		n.s.
Sayed, 2008 [41]	to controls		0.001
Shaaban, 2008 [56]			<0.05
Wang, 2008 [45]			<0.001
Bhagat, 2007 (SWL) [54]			0.3
Gravas, 2007 (SWL) [55]			0.02
Gravina, 2005 (SWL) [55]			<0.001
Han, 2006 (SWL) [33]			0.04
Mukhtarov, 2007 (SWL) [38]			<0.001
Colic episodes (%)			
Perron, 2008 [39]	7.94	7.89	n.s.
Porpiglia, 2008 [40]	1.4	1.1	n.s.
Resim, 2005 [24]	2	2.5	0.038
Sayed, 2008 [41]	1.5	2.5	0.003
Resim, 2005 (SWL) [24]	0	1	<0.01
Wang, 2008 (SWL) [69]	5	20	<0.05
Hospitalisation (%)			
Autorino, 2005 [25]	9	21	0.01
Dellabella, 2003 [20]	0	33	<0.0001
Dellabella, 2005 [28]	1.4	34.3	<0.004
De Sio, 2006 [29]	10	27.5	0.01
Erturhan, 2007 [35]	3.3	6.6	n.s.
Work days lost			
Dellabella, 2005 [25]	2	5	<0.0001

n.s. = not significant; SWL = shock wave lithotripsy.

Table 3 – Differences in analgesic requirements, emergency room visits, hospitalisation rates, and work days lost between treatment groups and controls

	Nifedipine vs control		*p* value
Analgesic requirements			
Dellabella, 2005 [28]	Analgesic requirements were lower for all calcium channel blocker studies compared to controls		<0.0001
Porpiglia, 2002 [62]			<0.05
Porpiglia, 2004 [21]			<0.0001
Porpiglia, 2002 (SWL) [62]			0.02
Emergency room visits			
Cooper, 2000 [47]	2.9	11.4	n.a.
Hospitalisation (%)			
Dellabella, 2005 [28]	20	34.3	<0.004
Work days lost			
Cooper, 2000 [47]	1.8	5	0.024
Dellabella, 2005	3	5	0.003

SWL = shock wave lithotripsy; n.a. = not available.

reported 12% adverse events in the alfuzosin group compared to 0% in the placebo group [17], whereas Yilmaz et al [27] and Liatsikos et al [37] reported no serious adverse events.

3.6. Hospitalisation rates

Hospitalisation rates were significantly reduced in four trials investigating tamsulosin [20,25,28,29] but were similar between groups in the study of Erturhan et al (Tables 2 and 3) [35]. In nifedipine versus phloroglucinol, hospitalisation rates were reduced from 34.3% to 20% [28]. Emergency room visits and work days lost were significantly reduced in patients receiving nifedipine or tamsulosin and prednisone [28,47].

3.7. Analgesic requirements

The vast majority of studies performed report a significant reduction in analgesic requirements (85%) or the number of colic episodes (71%) for nifedipine, tamsulosin, doxazosin, and terazosin (Tables 2 and 3).

3.8. Discussion

Results from this systematic review demonstrate evidence for a higher stone expulsion rate and a reduced time to stone expulsion using α-blocker or calcium channel blockers compared to a standard therapy or placebo control group. The beneficial expulsive effect was similar for α-blockade and calcium channel blockade for both higher expulsion rates and decreased expulsion time. Yilmaz et al observed similar expulsion rates and lower analgesic requirements in three different α-blockers, suggesting a class effect [27]. Only one alfuzosin trial reported unfavourable outcomes for the treatment group, although differences were not significant [17]. Nevertheless, the time to stone expulsion ($p = 0.003$) and the pain score ($p = 0.0005$) were significantly in favour of the treatment group. Notably, besides a possible lower effectiveness of alfuzosin, a small mean stone size in the placebo arm of 4.07 mm could have accounted for high spontaneous stone passage rates, leading to an underestimation of alfuzosin in promoting stone passage [17].

3.8.1. Stone size and medical expulsive therapy

Of nine α-blocker trials [23,33,34,37–39,43,47] investigating stone expulsion with mean stone sizes <5 mm, only four studies demonstrated a significantly higher expulsion rate in the treatment group [33,34,37,47]. In contrast, regarding α-blocker trials with stone sizes ≥5 mm, 19 of 20 studies demonstrated a significant benefit in stone expulsion rates mirrored by an increase of the ARR from 0.15 to 0.31. Although limited numbers of patients might account for undetectably significant differences in the treatment of smaller stones, results might as well indicate that with decreasing stone size, an additional benefit for MET is less likely because of the high spontaneous expulsion rate. Accordingly, although all α-blocker studies demonstrated a favourable expulsion time (Table 1), the study with the smallest mean stone diameter (2.9 vs 3.2) also demonstrated the smallest improvement in expulsion time (9.6 vs 10.1 d) [43]. This finding is supported by Liatsikos et al, demonstrating a relative lower efficacy of stone expulsion rates for <5-mm stones than for stones measuring 5–10 mm [37].

Similar observations where reported from shock wave lithotripsy (SWL) studies, suggesting an adjunct role of α-blocker to SWL. Bhagat et al [54]and Gravina et al [52] found no significant difference in stone-free rates in 6–10-mm ureteral stones. However, with increasing stone size ≥11 mm, the difference became significant. Similar findings have been reported by Küpeli et al [23]. The difference in expulsion rates between treatment and control groups for stones <5 mm was not significant. In contrast, stone-free rates in patients treated for stones >5 mm were significantly in favour of the treatment group. Porpiglia et al demonstrated that the average stone size between stone-free versus non–stone-free patients receiving nifedipine after SWL was not significantly different (11.8 mm vs 11.4 mm) [61]. In contrast, average stone size in stone-free versus non–stone-free patients in the control group was significantly different (8.8 mm vs 11.5 mm; $p = 0.002$), suggesting facilitated stone passage for larger stones in the nifedipine group.

3.8.2. Tamsulosin versus nifedipine in medical expulsive therapy

To date, three studies have compared the efficacy of tamsulosin versus nifedipine for distal ureteral stones [20,21,32]. Keshvary et al found no statistical difference in expulsion rates between tamsulosin and nifedipine [32]. Porpiglia et al evaluated the effectiveness of tamsulosin versus nifedipine in combination with deflazacort for stones <10 mm. Expulsion rates and expulsion time were in favour of the tamsulosin group, although differences were not significant [21]. Dellabella et al compared the efficacy of

tamsulosin and nifedipine in combination with deflazacort for stones >4 mm and demonstrated a significantly higher expulsion rate ($p = 0.001$) and shorter expulsion time ($p < 0.0001$) in the tamsulosin group, although stones in the tamsulosin group were significantly larger (7.2 mm vs 6.2 mm) [20]. Notably, the finding that stone size did not correlate with expulsion time might be attributable to the concomitant administration of a corticosteroid. Necessary hospitalisations, endoscopic procedures, analgesic requirements, and work days lost were significantly in favour of the tamsulosin group (Tables 2 and 3). The frequency of side-effects observed was not different between groups and did not result in treatment discontinuation.

3.8.3. Shock wave lithotripsy and medical expulsive therapy

Assuming that management of ureteral stones after ESWL for renal stones would not be different from that of ureteral stones, MET should be effective. Pooled data for α-blockers as adjunctive therapy after SWL suggest a treatment benefit for ureteral stones. All tamsulosin 0.4 mg, doxazosin, and terazosin trials demonstrated a higher stone-free rate, suggesting a class effect. Additionally, colic episodes or analgesic doses in the α-blocker groups were significantly lower in six out of seven trials (Table 2). Only one tamsulosin 0.2 mg trial after SWL reported lower stone-free rates for the treatment group, although differences were not significant. Nevertheless, the mean time to stone expulsion was significantly in favour of the treatment group (15.7 ± 6.1 d vs 35.5 ± 53.7 d; $p = 0.04$) [57].

All three studies available for renal stones treated with SWL have demonstrated higher stone-free rates with adjuvant α-blockade [52,54,59]. With respect to the control group, clearance rates after SWL were relatively higher after 1 mo compared to 3-mo follow-up. This finding suggests that larger fragments in the tamsulosin group were expelled, resulting in a favourable success rate after one SWL session compared to control groups necessitating further SWL sessions. Therapy with α-blockers could prove beneficial also for proximal ureteral stone locations, as they mediate a reduction in proximal ureteral tone of 33% [64]. Furthermore, all fragments have to pass the distal ureter; therefore, stone passage might be facilitated with a decreased expulsion time and fewer colicky episodes. Indeed, findings suggest a beneficial effect. Han et al administered tamsulosin for upper ureteral stones after SWL and found a significantly increased expulsion rate and significantly decreased analgesic requirements compared to a control group [65]. Porpiglia et al demonstrated a relatively higher expulsion rate for upper ureteral stones compared to a control group using nifedipine in conjunction with a corticosteroid [61]. The expulsion rate in the treatment group was equal for upper and distal ureteral stones.

As demonstrated, the adjuvant use of MET after SWL leads to increased expulsion rates, further reducing differences in success between SWL and ureteroscopy (URS). A question that has not been addressed so far is a possible benefit of neoadjuvant α-blockade or calcium channel blockade for patients undergoing SWL or ureterorenoscopic treatment. It has recently been suggested that increasing impaction has a negative influential effect on SWL and URS outcome [63,66–68]. Therefore, early administration of drugs counteracting ureteral spasm eventually in combination with corticosteroids may be beneficial and would deserve further evaluation.

3.8.4. Corticosteroids and combination therapy in medical expulsive therapy

Whether corticosteroids and tamsulosin alone or in combination effectively influence stone expulsion rates has recently been investigated [30]. The study period was 10 d, limiting side-effects caused by corticosteroids. Of interest—although stone expulsion rates in the corticosteroid group were comparable to a control group treated with analgesics only—a significant difference in favour of the combined tamsulosin–corticosteroid regimen was observed. This finding is supported by Dellabella et al, who did not find any correlation between stone size and time to stone expulsion when comparing three different drugs for MET (phloroglucinol, tamsulosin, and nifedipine), each administered with a corticosteroid, antibiotic, and NSAID [28]. The authors suggested that this phenomenon could be explained by the action of deflazacort, which decreases inflammation effects resulting from stone impaction.

Another trial from the same group assessed the efficacy of tamsulosin compared to tamsulosin plus deflazacort 30 mg for 10 d in distal ureterolithiasis [69]. Both groups demonstrated similar expulsion rates of 90% and 96.7%, but the expulsion time was significantly reduced in the combination therapy arm ($p = 0.036$). These findings suggest a benefit of combination therapy with corticosteroids and α-blockers but at the same time discourage the single use of corticosteroids.

3.8.5. Adverse events in medical expulsive therapy

Adverse events rarely led to drop-outs and were reversible after discontinuation of the drug (Table 1). Drop-out rates might have been low in trials with previous exclusion of patients prone to side-effects of the drugs used (eg, hypotensive patients) [21,46,49]. Inclusion of various drugs for standard treatment or steroids added to treatment groups possibly accounted for additional adverse events. The inconsistent reporting of adverse events and frequent nonreporting of minor adverse events render a final assessment in favour for nifedipine or α-blockers difficult. However, urologists possibly prefer using α-blockers for MET, as they are experienced with this class of drugs and their adverse event profile. Nevertheless, patients should be counselled on the attendant risks of MET, including associated drug side-effects, and should be informed that it is administered for an ‘‘off-label’’ use.

3.8.6. Limitations

Most studies were predominantly small, single-institution studies without previous power calculations (Table 1). The vast majority of randomised studies incorporated into the present systematic review is not blinded, with an

inadequately or unclear allocation concealment leading to a tendency towards overestimating the effectiveness of treatment effects [15], thus limiting the strength of our conclusions.

Heterogeneity within selected studies complicates integration. Clinical heterogeneity was expected, including trials using different drugs with the same class effect, different doses, or different formulations. Additionally, the frequent use of adjunctive medication potentially increased the degree of clinical heterogeneity. Moreover, differences in stone size and in stone size measurement using frontal kidney urinary bladder radiographs or computed tomography with different reconstructions potentially contribute to further heterogeneity. Additional factors possibly increasing heterogeneity between studies were the difference in time intervals from a colic episode to initiation of MET, the combination of blinded and nonblinded trials, insufficient or unclear allocation concealment, different durations of MET, and different follow-up periods defining treatment success or failure. Moderate heterogeneity was detected, questioning whether it is appropriate to pool the results (Figs. 2 and 10). However, excluding two studies [26,44] in Fig. 2 with unusually low stone expulsion rates in the control group or excluding one study [57] in Fig. 10 with excellent overall stone-free rates after SWL eliminated heterogeneity while maintaining RRs ($P = 0.16$; $I^2 = 21\%$; RR: 1.42; 95% CI: 1.33–1.52) and ($P = 0.5$; $I^2 = 0\%$; RR: 1.31; 95% CI: 1.21–1.42).

The presence of publication bias as demonstrated in funnel plot asymmetry in part limits the interpretation of our results. Failure to publish is not a random event but is influenced by research findings; hence, manuscripts demonstrating significant "positive" results will have a greater probability to be published, leading to an overestimation of treatment effects [70].

The adjunctive usage of various medications for MET theoretically could have an influential effect on treatment outcomes in either overestimation or underestimation of treatment effects. The concurrent use of corticosteroids with combination therapy of tamsulosin [69] or nifedipine [28,30] influenced expulsion rates. The treatment effect of tamsulosin or nifedipine could be overestimated because of a suspected synergistic effect of corticosteroids on stone expulsion. However, standard treatments were accepted as control groups, because an influential effect on stone expulsion for neither regimen has been demonstrated so far.

4. Conclusions

Evidence suggests that MET using nifedipine, tamsulosin, doxazosin, or terazosin can be suggested as treatment for ureteral stones owing to its expulsive efficacy, pain reduction, and safety profile. No recommendation can be made concerning the superiority of either nifedipine or α-blockers. Although a class effect of α-blockers can be anticipated, no recommendation can be made concerning alfuzosin. There is some evidence that a combination of α-blockers and corticosteroids might be more effective than treatment with α-blockers alone. The highest stone expulsion rates in distal ureteral stones were achieved using tamsulosin in combination with a corticosteroid.

Patients harbouring stones of up to 10 mm and eligible for observation may be offered MET. With increasing stone size >5 mm, the advantage of MET with α-blockers compared to a control group becomes emphasised. Although patients with ureteral stones >10 mm could be observed or treated with MET, no recommendation can be made at this point.

After SWL for ureteral stones, MET can be suggested using nifedipine, tamsulosin, doxazosin, and alfuzosin. Additionally, tamsulosin can be recommended after SWL treatment for renal pelvis as well as mid- and upper caliceal stones. Although the level of evidence for MET is high, the lack of multicentre, randomised, placebo-controlled studies with larger numbers of patients possibly results in an enhancement of the expulsive properties of the tested drugs. High-quality trials are needed to confirm the results obtained in this systematic review.

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Study concept and design: Seitz, Liatsikos, Porpiglia, Tiselius, Zwergel.
Acquisition of data: Seitz.
Analysis and interpretation of data: Seitz.
Drafting of the manuscript: Seitz.
Critical revision of the manuscript for important intellectual content: Seitz, Liatsikos, Porpiglia, Tiselius, Zwergel.
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