A Systematic Review of Medical Therapy to Facilitate Passage of Ureteral Calculi

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Study objective: Acute renal colic is a common presenting complaint to the emergency department. Recently, medical expulsive therapy using α-antagonists or calcium channel blockers has been shown to augment stone passage rates of moderately sized, distal, ureteral stones. Herein is a systematic evaluation of the use of medical expulsive therapy to facilitate ureteral stone expulsion.

Methods: We searched the databases of MEDLINE, EMBASE, and the Cochrane Controlled Trials Register. Additional sources included key urologic journals and bibliographies of selected articles. We included studies that incorporated a randomized or controlled clinical trial design, patients older than 18 years, treatment in which an α-antagonist or calcium channel blocker was compared to a standard therapy group, and studies that reported stone expulsion rates. A random effects model was used to obtain summary risk ratios (RRs) and 95% confidence intervals (CIs) for stone expulsion rate.

Results: A pooled analysis of 16 studies using an α-antagonist and 9 studies using a calcium channel blocker suggested that the addition of these agents compared to standard therapy significantly improved spontaneous stone expulsion (α-antagonist RR 1.59; 95% CI 1.44 to 1.75; number needed to treat 3.3 [95% CI 2.1 to 4.5]; calcium channel blocker RR 1.50; 95% CI 1.34 to 1.68; number needed to treat 3.9 [95% CI 3.2 to 4.6]) in patients with distal ureteral stones. Subgroup analysis of trials using concomitant medications (ie, low-dose steroids, antibiotics, and elimination of trials using an anticholinergic agent) yielded a similar improvement in stone expulsion rate. Adverse effects were noted in 4% of patients receiving α-antagonist and in 15.2% of patients receiving calcium channel blockers.

Conclusion: Our results suggest that "medical expulsive therapy," using either α-antagonists or calcium channel blockers, augments the stone expulsion rate compared to standard therapy for moderately sized distal ureteral stones. [Ann Emerg Med. 2007;50:552-563.]

0196-0644/$-see front matter

doi:10.1016/j.annemergmed.2007.05.015

INTRODUCTION

Background and Importance

The incidence of kidney stones in the general population appears to be increasing, as does the medical cost associated with this disease.[1,2] The number of primary outpatient visits, emergency department (ED) encounters, and the total estimated annual expenditure for individuals with claims for a diagnosis of urolithiasis have all doubled from 1994 to 2000, which translates into nearly 2 million primary outpatient visits, roughly 600,000 ED encounters, and approximately $2.1 billion in health care–related expenditures.[3]

The majority of individuals with urolithiasis have small (<5 mm) stones, located in the distal ureter, that are able to pass spontaneously. Both stone expulsion and time to expulsion of ureteral stones depend heavily on stone size and location.[4-10] Urologic intervention is recommended for ureteral stones that persist for more than 2 months.[11]

Recently, a number of small studies have demonstrated that α-antagonists and calcium channel blockers can be used to augment spontaneous stone expulsion and improve time to expulsion of distal ureteral stones. Interest in these agents stems from the understanding that ureteral smooth muscle contraction is driven by an increase in intracellular calcium and is modulated by the autonomic nervous system. Both α-antagonists and calcium channel blockers have been shown to inhibit the contraction of ureteral muscle responsible

for ureteral spasms while allowing antegrade stone propagation.[12-16]

Goals of This Investigation

The purpose of this systematic review is to critically evaluate the current body of evidence on medical therapy with α-antagonists and calcium channel blockers to facilitate spontaneous passage of distal ureteral calculi in adults. The primary outcome of interest is the proportion of patients who passed stones (ie, stone expulsion rate) with the addition of medical expulsive therapy compared with patients not receiving medical expulsive therapy. A secondary outcome of time to stone expulsion is also explored. Reported adverse effects are summarized and described.

MATERIALS AND METHODS

Study Design

The design and results of this systematic review conform to the recommendations from the Quality of Reporting of Meta-Analysis Statement.[17]

Searching

A comprehensive literature search of the MEDLINE, EMBASE, and the Cochrane Controlled Trials Register from January 1980 to January 2007 was performed. In MEDLINE, the medical subject heading "urolithiasis" was combined, in an iterative fashion, with the following individual phrases or words: "expulsive therapy," "facilitated therapy," "medical therapy," "adjunctive therapy," "medical management," "calcium channel blocker," "nifedipine," "verapamil," "diltiazem," "alpha antagonist," "tamsulosin," "terazosin," "doxazosin," "alfuzosin," and "prazosin." The MEDLINE search was limited to human studies, adult patients, and randomized trials or controlled clinical trials. We had no language restrictions. When an article was identified that met inclusion criteria, we used the MEDLINE tool Related Articles to search for additional trials. After the initial MEDLINE search, the search strategy was replicated, without the limitations, within the databases of EMBASE and the Cochrane Controlled Trials Register for additional trials. Two authors (A.S., A.L.) performed independent searches to identify potentially relevant abstracts. Articles were included in the final analysis according to consensus opinion.

Additionally, a hand search was performed in the following urologic journals from January 2000 to January 2007: *Journal of Urology, Urology, International Journal of Urology, European Urology, British Journal of Urology, Canadian Journal of Urology*. The electronic Web site addresses of these journals were visited for potentially relevant articles that were published online ahead of their print date. The bibliographies of articles identified through electronic searches were reviewed for additional trials not previously identified. Finally, abstracts from major urologic conferences (American Urological Association, British Association of Urologic Surgeons, Canadian Urologic Association, European Association of Urology, World Congress of Endourology) in the past 7 years were scrutinized for supplementary data. We attempted to electronically contact the primary authors from published scientific abstracts for information about additional study data, including publication of completed analyses.

Selection

The following inclusion criteria were used to select articles for this review: (1) studies were randomized or controlled clinical trials, (2) patients were older that 18 years, (3) patients were clinically and radiographically diagnosed with acute ureteral colic, (4) therapy was begun in the inpatient or outpatient setting, including the ED, or on referral to a urologist, (5) medical expulsive therapy using an α-antagonist or calcium channel blocker was compared to a control group, (6) studies included the primary outcome of interest identified for this analysis.

Validity Assessment

Individual trial characteristics, including study design, conduct, data analysis, and interpretation, were reviewed using the revised CONSORT statement.[18] This 22-item checklist systematically analyzes the quality of reporting the results of parallel-group randomized trials. Additionally, quality was assessed using the Jadad scale for each reviewed study.[19] This validated scale ranges from 0 to 5, with a higher score indicative of a study that had adequate randomization, blinding, and follow-up of withdrawals and dropouts.

Data Abstraction

Independently and in duplicate, 2 of the authors abstracted data from selected trials (A.S., A.L.). Information abstracted included the objective, patient population, baseline patient characteristics, cointerventions, and study results. Discrepancies were discussed and resolved by consensus from these 2 authors.

Study Characteristics

We sought to include all potentially relevant trials using either an α-antagonist or calcium channel blocker as an adjuvant medical therapy to promote ureteral stone expulsion. We expected some degree of clinical heterogeneity in our results, given the inclusion of trials that used chemically different drugs with similar mechanisms of action (eg, terazosin, doxazosin) and matching drugs that used alternate formulations (eg, nifedipine immediate release, nifedipine sustained release). Similarly, the variable use of concomitant anticholinergic agents, low-dose steroids, and antibiotics was predicted to amplify the degree of expected heterogeneity.

Quantitative Data Synthesis

We calculated a pooled risk ratio (RR) and 95% confidence intervals (CIs) for the effects α-blocker and calcium channel blockers on stone expulsion rate by using the random-effects

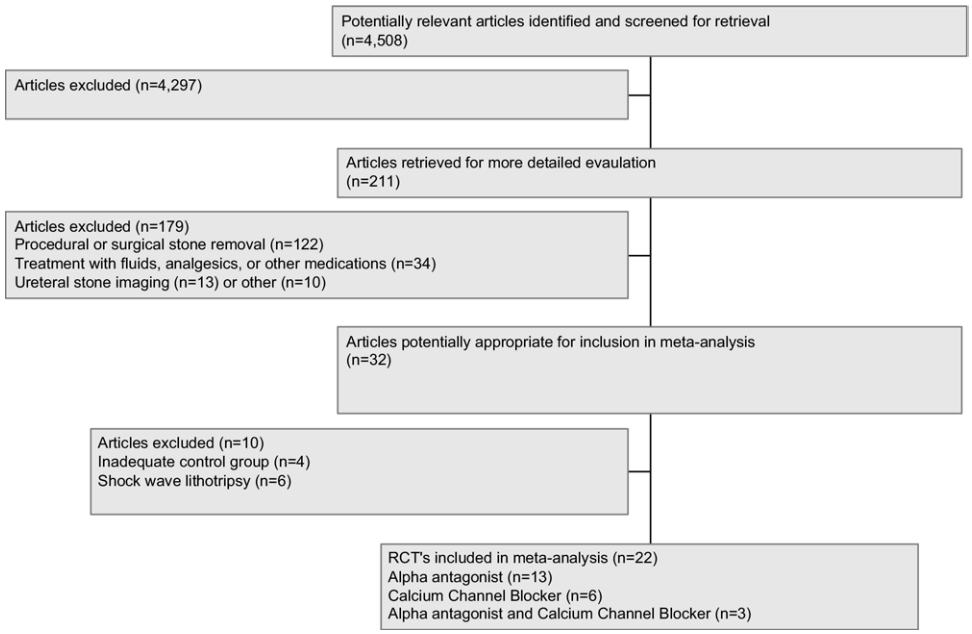

Figure 1. Trial flow diagram.

model described by Der Simonian and Laird.[20] This model was selected because it provides a conservative estimate or treatment effect. Heterogeneity was explored through the use of Cochrane Q test for heterogeneity (which follows a χ^2 distribution), an estimate of between-study variance known as τ^2, and an estimate of the amount of variance across studies due to heterogeneity rather than chance, known as I^2 statistic.[21] On the basis of the pooled RR, we calculated the number needed to treat. The 95% CIs for numbers needed to treat were calculated with the Newcombe-Wilson hybrid score method.[22] Publication bias was explored with the use of funnel plots,[23] the Egger regression asymmetry test,[24] and the Begg adjusted rank correlation test. We used Stata version 8.0 (StataCorp, College Station, TX) for all analyses.

We determined a priori that our sensitivity analysis should focus on the impact of poor-quality studies (ie, Jadad score <3). To assess the effect of individual studies on the summary RR, we did an influence analysis,[25] in which the pooled estimate was recalculated omitting 1 study at a time. Such a sensitivity analysis demonstrates robustness if all point estimates lie between the confidence limits of the overall summary estimate. Prespecified subgroup analysis included separate analysis of studies that included potential confounders (ie, anticholinergic agents, low-dose steroid, antibiotics), and those that used an α-antagonist besides tamsulosin.

RESULTS

Trial Flow

The initial MEDLINE search strategy identified 4,443 possible publications about urolithiasis. Electronic and hand searching for additional data revealed an additional 15 potentially relevant publications for inclusion. After application of the initial exclusion criteria to this search, the abstracts from a total of 211 clinical trials were reviewed (Figure 1). Trials involving procedural or surgical stone removal (n=122), treatment with fluids, analgesics, or other medications (n=34), ureteral imaging techniques (n=13), or unrelated conditions were excluded. The full articles of 32 trials were reviewed. At this level, studies were excluded because of inadequate control group[26-29] or trials involving the study drugs in the setting of shockwave lithotripsy.[30-35] The remaining 22 articles are included in this analysis.[36-57]

Study Characteristics

No articles followed the revised CONSORT statement guidelines for reporting of randomized controlled trials. Jadad scores ranged from 0 to 3 in all clinical trials reviewed, with a median score of 2 for both α-antagonist (Table 1) and calcium channel blocker trials (Table 2). Absence of double blinding was the most frequent reason for point deduction. Five scientific assembly abstracts were included in the final analysis.[40,45,49,55,56] We attempted to contact the authors of these 5 abstracts but received no response at the time of article submission.

Tamsulosin was the α-antagonist used in 13 of the 16 trials.[36-39,41-48,51] The results from trials that included other α-antagonists (eg, terazosin,[40,46,50] doxazosin[46,49]) were combined with the results of tamsulosin and were also analyzed independently. Nifedipine was the calcium channel blocker used in all 9 trials.[39,43,45,52-57] All the trials allowed for pain medications (commonly nonsteroidal anti-inflammatory

Table 1. Study characteristics of trials involving α-antagonists.

First Author, Year	Jadad Score			Cointerventions and Comparisons
	Randomization	Blinding	Follow-up	
Cervenakov, 2002[36]	1	0	1	Steroid-like agent and anxiolytic in treatment and control group
Dellabella, 2003[37]	1	0	1	Steroid and antibiotic in treatment and control group; anticholinergic agent in control group
Kupeli, 2004[38]	2	0	1	Subgroup of patients who did not undergo immediate shockwave lithotripsy
Porpiglia, 2004[39]	2	0	1	Steroid and gastroprotective agent in treatment group only
Tekin, 2004[40]	1	0	0	Control group with placebo only*
Autorino, 2005[41]	2	0	1	Steroid-like agent, gastroprotective agent, and antibiotic in treatment and control group
Avdoshin, 2005[42]	1	0	1	Anticholinergic agent in both treatment and control group; control group rate of stone expulsion <25%
Dellabella, 2005[43]	2	0	1	Steroid and antibiotic in treatment and control group; anticholinergic agent in control group
Resim, 2005[44]	1	0	1	Control group with placebo only
Taghavi, 2005[45]	1	0	0	Control group with placebo only*
Yilmaz, 2005[46]	1	0	1	Comparison of 3 α-antagonists without low-dose steroid. Control group with placebo only
DeSio, 2006[47]	2	0	1	Steroid-like agent, gastroprotective agent, and antibiotic in treatment and control group
Han, 2006[48]	1	0	1	Anticholinergic agent in control group
Liatsikos, 2006[49]	1	0	0	Control group with placebo only*
Mohseni, 2006[50]	1	0	1	Control group with placebo only
Porpiglia, 2006[51]	1	0	1	Subgroups with and without steroids for treatment and control group

*Abstract available only.

Table 2. Study characteristics of trials involving calcium channel blockers.

First Author, Year	Jadad Score			Cointerventions and Comparisons
	Randomization	Blinding	Follow-up	
Borghi, 1994[52]	1	2	1	Steroid in treatment and control group
Cooper, 2000[53]	1	0	1	Steroid, antibiotic, and acetaminophen in treatment group only; oxycodone/acetaminophen and prochlorperazine in treatment and control group
Porpiglia, 2000[54]	2	0	1	Steroid and gastroprotective agent in treatment group only
Staerman, 2000[55]	1	0	0	Anticholinergic agent in treatment and control group*
Skrekas, 2003[56]	1	0	0	Control group with placebo only*
Porpiglia, 2004[39]	2	0	1	Steroid and gastroprotective agent in treatment group only
Saita, 2004[57]	0	0	1	Steroid in treatment and control group
Dellabella, 2005[43]	2	0	1	Steroid and antibiotic in treatment and control group; anticholinergic agent in control group
Taghavi, 2005[45]	1	0	0	Control group with placebo only*

*Abstract available only.

medications) and encouraged a minimum of 2 L of fluid intake per day.

The median follow-up period from time of enrollment was 4 weeks (range 1 week to 7 weeks) for α-antagonist trials. Similarly, patients in the calcium channel blocker trials were evaluated a median of 4 weeks (range 3 weeks to 7 weeks) after enrollment.

In many of the trials, additional medications (eg, low-dose steroid or steroid-like agent, antibiotic, gastroprotective agent, anxiolytic, anticholinergic agent, antiemetic) were prescribed and were equally matched in the treatment group and standard therapy group. In 3 trials, 2 additional interventions (low-dose steroid plus either an antibiotic[53] or gastroprotective agent[39,54]) were present in the treatment group but not the standard therapy group. Aescin, an extract from horse chestnut seed, thought to have some steroid-like properties, was used as an adjunctive medication in 3 trials.[36,41,47] Additionally, in 5 trials, the standard therapy group received an anticholinergic agent that was postulated to augment stone expulsion.[37,42,43,48,55]

The reported stone expulsion rate from several studies was adjusted to reflect a worst-case scenario principle.[36,51,52,57] In these trials, unexplained dropouts were considered treatment failures. There were insufficient data to adjust the analysis for one trial.[55]

Table 3. Results of trials involving α-antagonist therapy.

First Author, Year	Enrollment Site	Duration of Follow-up	Intervention	Mean Stone Size, mm	Mean Time to Expulsion, Days	Stone Expulsion Rate (%)
Cervenakov, 2002[36]	Hospital admit	1 wk	Tamsulosin	NR	NR	41/51 (80)
			Control group			32/53* (60)
Dellabella, 2003[37]	ED	4 wk	Tamsulosin	6.7	2.7	30/30 (100)
			Control group	5.8	4.6	21/30 (70)
Kupeli, 2004[38]	Not specified	2 wk	Tamsulosin	4.7	NR	8/15 (53)
			Control group	4.9		3/15 (20)
Porpiglia, 2004[39]	Urology clinic	4 wk	Tamsulosin	5.4	7.9	24/28 (86)
			Control group	5.4	12	12/28 (43)
Tekin, 2004[40]	Not specified	4 wk	Terazosin	7.3	NR	28/36 (78)
			Control group	6.8		18/39 (46)
Autorino, 2005[41]	Urology clinic	4 wk	Tamsulosin	6.5	4.8	28/32 (88%)
			Control group	5.7	7.4	19/32 (59%)
Avdoshin, 2005[42]	Urology clinic	NR	Tamsulosin	7.4	NR	31/42 (74%)
			Control group	7.4		11/45 (24%)
Dellabella, 2005[43]	ED	4 wk	Tamsulosin	7.2	3	68/70 (97)
			Control group	6.2	5	45/70 (64)
Resim, 2005[44]	Urology clinic	6 wk	Tamsulosin	7.8	NR	26/30 (87)
			Control group	7.8		22/30 (73)
Taghavi, 2005[45]	Urology clinic	4 wk	Tamsulosin	6.7	8.2	18/20 (90)
			Control group	6.8	14.2	11/24 (46)
Yilmaz, 2005[46]	Not specified	4 wk	Tamsulosin	6.0	6.3	23/29 (79)
			Terazosin	6.0	5.8	22/28 (79)
			Doxazosin	5.9	5.9	22/29 (76)
			Control group	6.1	10.5	15/28 (54)
DeSio, 2006[47]	Urology clinic	2 wk	Tamsulosin	6.9	4.4	45/50 (90)
			Control group	6.4	7.5	27/46 (59)
Han, 2006[48]	Not specified	4 wk	Tamsulosin	4.4	4.6	29/35 (83)
			Control group	4.3	8.3	17/32 (53)
Liatsikos, 2006[49]	Not specified	4 wk	Doxazosin	NR	NR	25/30 (83)
			Control group			16/30 (53)
Mohseni, 2006[50]	ED	4 wk	Terazosin	6.9	3.2	29/32 (91)
			Control group	6.6	5.9	20/32 (63)
Porpiglia, 2006[51]	ED	7 wk	Tamsulosin	5.9	NR	51/66* (77)
			Control group	5.7		23/48 (48)

NR, Not reported.
*Denominator adjusted to reflect worst-case scenario principle.

Quantitative Data Synthesis

α-Antagonist. Pooled data included 1,235 patients from 16 clinical trials[36-51] (Table 3). The overall range of stone size was 3 mm to 18 mm, with a mean stone diameter greater than 5 mm in all trials except 2.[38,48] All studies evaluated stones located in the distal portion of the ureteral tract.

Although minimal heterogeneity existed in the group of α-antagonist studies using the Cochrane Q statistic (χ^2=21.32; P=.13) and τ^2 test (τ^2=.011), the I^2 statistic was 30% (95% CI 0% to 61%), suggesting a mild to moderate amount of across-study variance caused by heterogeneity.

The combined results of all trials using an α-antagonist suggest that a benefit in stone expulsion is achieved when combined with standard therapy (RR 1.59; 95% CI 1.44 to 1.75) (Figure 2). The number needed to treat is 3.3 (95% CI 2.1 to 4.5). The funnel plot visually demonstrated mild asymmetry (Figure 3). However, evidence for publication bias was suggested through analysis by Begg's test (P=.003) and Egger's test (t for bias=2.7; P=.02).

Nine trials evaluated time to stone expulsion (Table 3). In all 9 trials, a 2- to 6-day average improvement in time to stone expulsion was observed in patients receiving an α-antagonist compared with the control group. The mean time to stone expulsion in the treatment group, including the upper limit of the 95% CI, was less than 14 days in patients receiving an α-antagonist.

Adverse effects were not consistently reported for all the trials. Overall, adverse effects were observed in 4% of patients. Mild adverse effects included dizziness (n=6), headache (n=4), nausea/vomiting (n=2), asthenia (n=2), and not recorded (n=3). Transient hypotension, not requiring discontinuation of therapy, occurred in 8 patients. One patient experienced severe asthenia and discontinued therapy (0.2%).

Calcium channel blocker. Pooled data included 686 patients from 9 trials[39,43,45,52-57] (Table 4), with an average stone size greater than 5 mm in all trials except 3.[39,53,55] Each study evaluated stones in the distal ureter; however, 3 studies included stones within the upper and middle ureteral tract.[52,53,57]

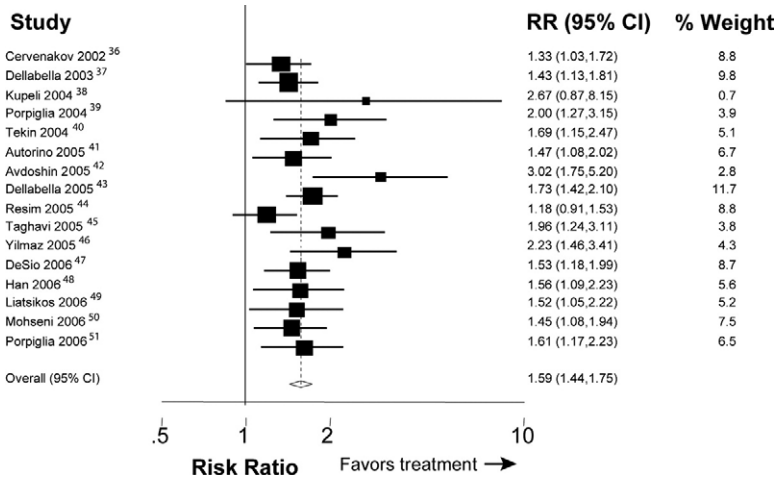

Figure 2. α-Antagonist forest plot. The central square of each horizontal line represents the RR for each study. The lines demonstrate the range of the 95% CI. The vertical line at an RR of 1 is the line of no effect. % Weight indicates the influence exerted by each study on the pooled RR.

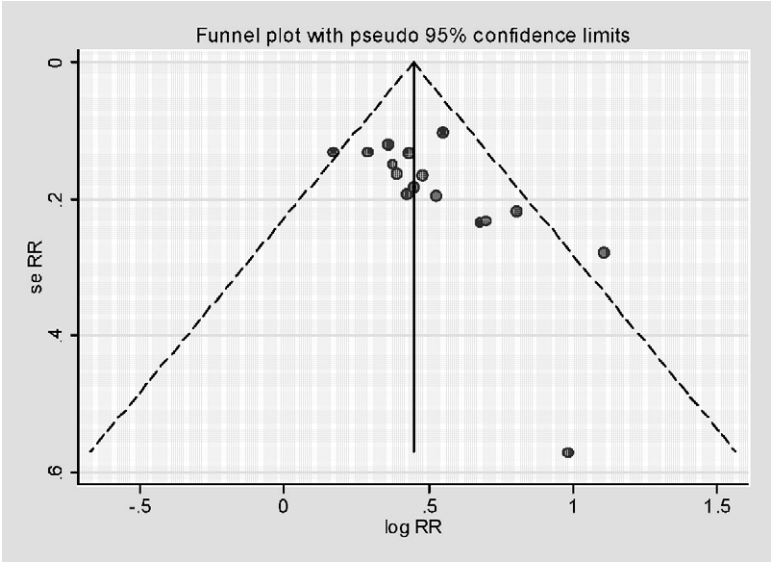

Figure 3. α-Antagonist funnel plot. Funnel plot for evaluation of publication bias. Vertical solid line represents the logarithmic transformation of the overall estimated treatment effect (ie, log [RR]), diagonal dotted lines represent pseudo–95% confidence limits for estimated treatment effect, and the circles represent treatment effects of each of the 16 studies. In the absence of publication bias, graph should represent a funnel, with individual studies clustered around the overall estimated treatment effect symmetrically.

Little heterogeneity existed in the group of calcium channel blocker studies. The Cochrane Q statistic (χ^2=6.73) was not significant (P=.566), there was minimal between study variance (τ^2=0.000), and the I^2 statistic was 0% (95% CI 0% to 65%).

The combined results of all trials using a calcium channel blocker suggest that a benefit in stone expulsion is achieved when combined with standard therapy (RR 1.50; 95% CI 1.34 to 1.68) (Figure 4). The number needed to treat is 3.9 (95% CI 3.2 to 4.6). Visual inspection of the funnel plot demonstrated mild asymmetry (Figure 5). There was no evidence for publication bias when data were analyzed by Begg's test (P=.35) or Egger's test (t for bias=1.1, P=.31).

All 9 calcium channel blocker trials evaluated time to stone expulsion (Table 4). When compared to standard therapy, a reduction in time to stone expulsion was observed in 7 of these trials. The mean time to stone expulsion in the treatment group, including the upper limit of the 95% CI, was less than 28 days in these trials.

Adverse effects were not consistently reported for all the trials. Overall, adverse effects were observed in 15.2% of patients in these trials. Mild adverse effects included nausea/vomiting (n=11), asthenia (n=10), dyspepsia (n=6), headache (n=3), drowsiness (n=4), euphoria (n=2), and not reported (n=3).

Table 4. Results of trials involving calcium channel blocker therapy.

First Author, Year	Enrollment Site	Duration of Follow-up	Intervention	Mean Stone Size, mm	Mean Time to Expulsion, Days	Stone Expulsion Rate (%)
Borghi, 1994[52]	ED	7 wk	Nifedipine	6.7	11.2	34/43* (79%)
			Control group	6.8	16.4	24/43* (56%)
Cooper, 2000[53]	Urology clinic	7 wk	Nifedipine	3.9	12.6	31/35 (89%)
			Control group	3.9	11.2	19/35 (54%)
Porpiglia, 2000[54]	Urology clinic	4 wk	Nifedipine	5.8	7	38/48 (79%)
			Control group	5.5	20	17/48 (35%)
Staerman, 2000[55]	Hospital admit	NR	Nifedipine	4.5	5.1	21/25 (84%)
			Control group	4.3	12.9	16/25 (64%)
Skrekas, 2003[56]	Not specified	4 wk	Nifedipine	5.0	6	38/46 (83%)
			Control group	5.5	18	26/46 (57%)
Porpiglia, 2004[39]	Urology clinic	4 wk	Nifedipine	4.7	9.3	24/30 (80%)
			Control group	5.4	12	12/28 (43%)
Saita, 2004[57]	Urology clinic	3 wk	Nifedipine	12.0	6	15/25* (60%)
			Control group	12.8	10	12/25* (48%)
Dellabella, 2005[43]	ED	4 wk	Nifedipine	6.2	5	54/70 (77%)
			Control group	6.2	5	45/70 (64%)
Taghavi, 2005[45]	Urology clinic	4 wk	Nifedipine	6.4	10	14/20 (70%)
			Control group	6.8	14.2	11/24 (46%)

*Denominator adjusted to reflect worst-case scenario principle.

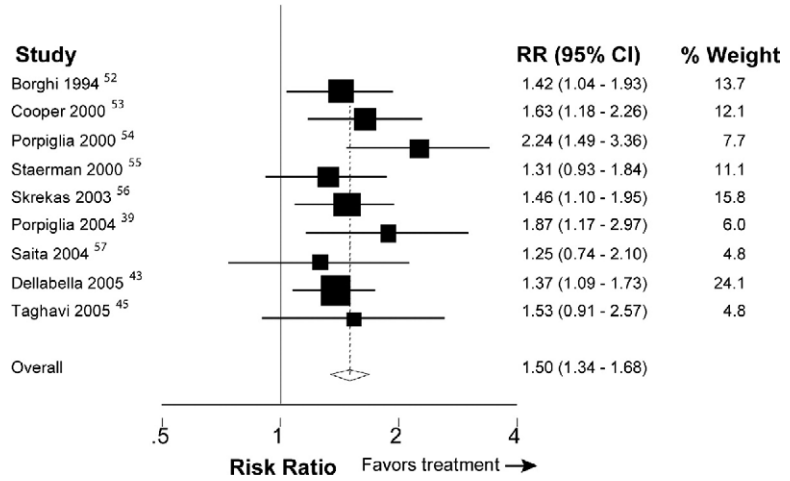

Figure 4. Calcium channel blocker forest plot. Refer to legend in Figure 2 for explanation.

Transient hypotension, not requiring discontinuation of therapy, occurred in 3 patients. A total of 10 patients discontinued therapy (2.9%). Of these patients, 4 experienced hypotension or palpitations and 6 experienced erythema or edema. The mean decrease in systolic blood pressure was 15 mm Hg (range 10 to 25 mm Hg), mean decrease in diastolic blood pressure was 8 mm Hg, and the mean increase in pulse rate was 8 beats/min.[52,54]

Sensitivity and Subgroup Analysis

Our sensitivity analysis of α-antagonist and calcium channel blocker trials focused on the impact of poor-quality studies (ie, Jadad score <3) on the overall RR. A pooled analysis of 386 patients in 5 α-antagonist trials,[38,39,41,43,47] whose Jadad score was greater than or equal to 3, resulted in an RR of 1.66 (95% CI 1.45 to 1.89). Similarly, a pooled analysis of 380 patients in 4 calcium channel blocker trials,[39,43,52,54] whose Jadad score was greater than or equal to 3, resulted in an RR of 1.60 (95% CI 1.28 to 2.01).

Sequential exclusion of each study from the analysis of α-antagonist trials resulted in minor changes in the pooled RR or precision of the effect estimates, including exclusion of the study with the most influence, Avdoshin et al,[42] which resulted in an RR of 1.54 (95% CI 1.42 to 1.68). Elimination of this study from the pooled analysis reduced the summary I^2 statistic for α-antagonist studies to 5%. Identically, sequential exclusion of each study from the analysis of calcium channel blocker trials resulted in minimal changes in the pooled RR or precision. Elimination of the study with the most influence, Porpiglia et al,[54] resulted in an RR of 1.45 (95% CI 1.29 to 1.63).

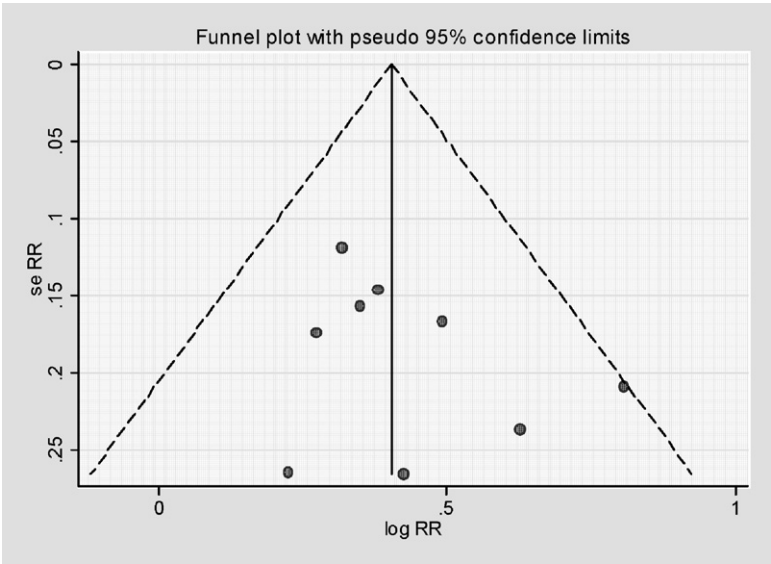

Figure 5. Calcium channel blocker funnel plot. Refer to legend in Figure 3 for explanation.

Table 5. Results of α-antagonist subgroup analysis.

α-Antagonist Subgroup Characteristics	n=# Trials, # Patients	RR Stone Expulsion (95% CI)
All trials except those using an anticholinergic agent[36,38-41,44-47,49-51]	n=12, 881	1.61 (1.41–1.85)
Trials using steroid or steroidlike agent in treatment and control group[36,37,41,43,47,51]	n=6, 521	1.56 (1.36–1.79)
Trials using steroid and antibiotic in treatment and control group[37,41,43,47]	n=4, 360	1.60 (1.43–1.80)
Trials with no steroid use in either treatment or control group[38,40,42,44-46,48-51]	n=10, 658	1.62 (1.32–1.97)
Trials using α-antagonist besides tamsulosin[40,46,49,50]	n=4, 284	1.65 (1.37–1.99)
Trials with Jadad score $\geq$3[38,39,41,43,47]	n=5, 386	1.66 (1.45–1.89)

Table 6. Results of calcium channel blocker subgroup analysis.

Calcium Channel-Blocker Subgroup Characteristics	n=# Trials, # Patients	RR Stone Expulsion (95% CI)
All trials except those using an anticholinergic agent[39,45,52-54,56,57]	n=7, 496	1.58 (1.37–1.82)
Trials using steroid or steroid-like agent in treatment and control group[43,52,57]	n=3, 276	1.37 (1.15–1.63)
Trials using steroid in treatment group only[39,53,54]	n=3, 224	1.85 (1.48–2.31)
Trials with no steroid use in either treatment or control group[45,55,56]	n=3, 186	1.42 (1.16–1.73)
Trials with Jadad Score $\geq$3[39,43,52,54]	n=4, 380	1.60 (1.28–2.01)

Our subgroup analysis of the use of α-antagonists and calcium channel blockers focused on the impact of several potentially confounding medications (ie, anticholinergic agents, low-dose steroids, antibiotics) and the use of an α-antagonist besides tamsulosin on the overall summary RR (Table 5 and Table 6). Minor changes to the overall relative risk were noted when these groups were analyzed independently.

LIMITATIONS

Up to one third of meta-analyses purporting successful therapy are later discredited after a large-scale, well-done, randomized, controlled trial is completed.[58] Thus, the results of using the meta-analysis study methodology to address a clinical question must be interpreted with caution. An advantage of the meta-analyses is to combine underpowered studies to increase the sample size and confidence of the results. However, aggregate results incorporate the biases of individual trials and evoke new sources of bias because of study selection and heterogeneity.

We anticipated some degree of heterogeneity when combining trials that were both clinically and methodologically diverse. Using the I^2 statistic, we identified a mild to moderate amount of across-study variance caused by heterogeneity in the trials that evaluated α-antagonists. Elimination of a single study[42] from the analysis significantly reduced this concern and had a diminutive effect on the overall RR. In this study, the rate of stone expulsion in the control group was significantly less

than that reported in other studies, resulting in, perhaps, an artificially increased RR.

The median Jadad score of 2 for all trials reflected the poor overall quality of studies reviewed. The absence of using a double-blinded methodology in the majority of trials reviewed and the lack of appropriate randomization in several trials limit the strength of our conclusions. Additionally, given the small numbers of patients enrolled in these studies, the inability to adjust for differences in factors beyond the reported baseline characteristics could have influenced the outcome reported within this study.

Although we attempted to limit bias by using an extensive search strategy, our results are limited by publication bias, which may lead to overestimation of treatment effect. In our analysis the α-antagonist and calcium channel blocker funnel plots demonstrated some amount of asymmetry by visual inspection, indicating potential publication bias. However, funnel plot asymmetry is also observed with conditions other than publication bias and can be seen, as is demonstrated by our data, when smaller studies within a meta-analysis demonstrate larger treatment effects.[59,60] The results from Begg's test and Egger's test indicated a lack of publication bias in trials using calcium channel blockers but demonstrated evidence of publication bias in trials evaluating α-antagonists. We were unable to identify any article or scientific abstract data suggesting negative or neutral results with the use of α-antagonists. A contemporary move by major medical journals requiring authors to preregister randomized trials as a prerequisite for publication is anticipated to reduce the amount of publication bias in future meta-analyses.

The location of patient enrollment and follow-up time potentially hinder the application of these results to the ED. Indeed, a majority of trials included patients referred to a urologist, presumably after a previous evaluation by an emergency or primary care physician. Compared to patients who do not keep their urology appointment, patients who keep their appointment may reflect a subgroup less likely to experience spontaneous stone expulsion. However, there are no trials supporting the concept that the stone expulsion rate is different between patients evaluated in the ED and those evaluated at urologic follow-up. Furthermore, the majority of ureteral stones evaluated in these studies were greater than 5 mm, which is a group that is expected to have poor stone expulsion rates regardless of the site of patient enrollment.

DISCUSSION

The results of this meta-analysis suggest a significant benefit in the stone expulsion rate when either an α-antagonist or calcium channel blocker is added to standard therapy in the medical management of moderately sized distal ureteral stones. During a period of watchful waiting, patients may experience complications such as repeated renal colic, urinary infection, and hydronephrosis, all of which may prompt repeated evaluation. Alternatively, early endoscopic treatment with ureteroscopy or extracorporeal shockwave lithotripsy greatly improves stone passage rates. These procedures, however, are not risk free,[61-68] require referral for urologic expertise, and are more costly than the watchful waiting approach.[69]

Previous clinical reports describing the use of these agents in ureteral colic have focused on nifedipine for the treatment of pain.[70-77] Our analysis focuses on trials that have evaluated the role of medical expulsive therapy in facilitating stone expulsion. Our results mirror those of a previous meta-analysis[78] and several nonsystematic reviews on the same subject.[79-88] Compared to a previous meta-analysis, our database included 7 additional α-antagonist trials[41,42,47-51] and 1 additional calcium channel blocker trial.[57] Additionally, our results are stratified by type of medication used, as opposed to combining α-antagonist and calcium channel blocker therapy. The summary RR obtained for medical expulsive therapy between our study and the previous meta-analyses is similar.

The results of this analysis demonstrate significant benefit when adjusted for the presence of confounding interventions (eg, anticholinergics, low-dose steroids, antibiotics) and elimination of lower-quality trials (Jadad score <3). Additionally, the overall time to stone expulsion was improved with the addition of either medication. However, several unanswered questions about ureteral stone size, stone location, concurrent use of adjunctive medication, and use of an α-antagonist other than tamsulosin deserve further consideration.

Small, less than 5-mm distal ureteral stones, will most likely spontaneously pass within 4 weeks, without the need for urologic intervention.[4-10] Separate analysis of 2 studies with tamsulosin[38,48] and analysis of 3 studies with nifedipine[39,52,53] for stones up to 5 mm suggest some improvement in the stone expulsion rate and time to expulsion with the addition of either agent. However, the small number of patients in these studies does not allow any definitive conclusion about cost-to-benefit analysis in these patients.

To our knowledge, there are no trials on medical expulsive therapy that specifically address large, greater than 10-mm ureteral stones in the absence of shockwave lithotripsy. The results of trials on medical expulsive therapy in patients concomitantly treated with shockwave lithotripsy suggest benefit of nifedipine[30,31] and tamsulosin[31-35,38] in this setting.

A single study[89] and subgroup analysis of another study[51] have directly evaluated the role of steroids without adjunctive medication to facilitate ureteral stone expulsion, with mixed results. The addition of a low-dose steroid is thought to prevent edema around the ureteral stone and slowing of stone passage. The results of 2 trials comparing stone passage rates in patients receiving tamsulosin plus low-dose steroid to tamsulosin alone were mixed.[29,51] Given the inconsistency of these results, no firm conclusion about the efficacy of adding low-dose steroids to medical expulsive therapy can be made.

Prophylactic antibiotics were commonly used in these studies to prevent urinary tract infection from developing and slowing stone passage. Separate analysis of steroid trials that also

included the addition of an antibiotic suggests marginal benefit when either of these agents is added to tamsulosin.

The most commonly used agent was tamsulosin 0.4 mg taken daily for 1 month; however, in several trials, terazosin (5 to 10 mg daily by mouth)[40,46,50] and doxazosin (4 mg daily by mouth)[46,49] were used with similar efficacy. The success of these trials and of uncontrolled trials with doxazosin[26] and alfuzosin[27,28] suggests that the benefit of α-antagonists may be a class effect and not specific to tamsulosin. To our knowledge, no other calcium channel blocker has published data validating its use for medical expulsive therapy, although experimental data with diltiazem and verapamil suggest that these agents may also be helpful.[13,14] We found no trials evaluating the combination of α-antagonist to calcium channel blocker to facilitate stone passage. Furthermore, no data exist on the addition of either therapy when combined with β-adrenergic antagonists[90] or glyceryl trinitrate.[91]

A 1-month follow-up period was selected by the majority of authors according to current urologic practice and recommendations.[11] During this time, the use of an α-antagonist was associated with a 2- to 6-day reduction in time to stone expulsion. Similarly, the majority of trials evaluating calcium channel blockers reported an improvement in time to stone expulsion. The mean time to successful stone expulsion, including upper limit of the 95% CI, was fewer than 14 days in the α-antagonist trials and fewer than 28 days in the calcium channel-blocker trials, suggesting that a 2- to 4-week time course of these medications is warranted.

Both α-antagonists and calcium channel blockers are well tolerated, with minimal adverse effects. Overall, 4% of patients receiving α-antagonist and 15.2% of patients receiving calcium channel-blocker therapy experienced adverse effects. Only 1 patient (0.2%) required discontinuation of α-antagonist therapy during treatment, and 10 patients (2.9%) required discontinuation of calcium channel blocker therapy. No reports of impotence, ejaculatory failure, or decreased libido were reported with the short-course administration of an α-antagonist.

The results of this meta-analysis are encouraging for the use of an α-antagonist or calcium channel blocker to facilitate stone expulsion of moderately sized distal ureteral calculi; however, because of the limitations of methodologic quality within the studies reviewed, a large, well-done, randomized, clinical trial is needed to confirm these results before uniform adoption can be recommended.

We thank Rada Grin, MD, Highland General Hospital, for her assistance with the English translation of several articles; and Elaine Barnes, MLS, San Ramon Regional Medical Center, for her assistance in obtaining selected references.

Supervising editor: Peter C. Wyer, MD

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article, that might create any potential conflict of interest. The authors have stated that no such relationships exist. See the Manuscript Submission Agreement in this issue for examples of specific conflicts covered by this statement.

Publication dates: Received for publication February 8, 2007. Revisions received March 21, 2007; April 21, 2007; and May 6, 2007. Accepted for publication May 9, 2007. Available online August 3, 2007.

Reprints not available from the authors.

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