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Published in:
Annals of Emergency Medicine

DOI:
[10.1016/j.annemergmed.2015.06.001](https://doi.org/10.1016/j.annemergmed.2015.06.001)

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Recommended citation(APA):

Furyk, J. S., Chu, K., Banks, C., Greenslade, J. H., Keijzers, G., Thom, O., Torpie, T., Dux, C., & Narula, R. (2016). Distal Ureteric Stones and Tamsulosin: A double-blind, placebo-controlled, randomized, multicenter trial. *Annals of Emergency Medicine*, 67(1), 86-95e2. <https://doi.org/10.1016/j.annemergmed.2015.06.001>

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Distal Ureteric Stones and Tamsulosin: A Double-Blind, Placebo-Controlled, Randomized, Multicenter Trial

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Study objective: We assess the efficacy and safety of tamsulosin compared with placebo as medical expulsive therapy in patients with distal ureteric stones less than or equal to 10 mm in diameter.

Methods: This was a randomized, double-blind, placebo-controlled, multicenter trial of adult participants with calculus on computed tomography (CT). Patients were allocated to 0.4 mg of tamsulosin or placebo daily for 28 days. The primary outcomes were stone expulsion on CT at 28 days and time to stone expulsion.

Results: There were 403 patients randomized, 81.4% were men, and the median age was 46 years. The median stone size was 4.0 mm in the tamsulosin group and 3.7 mm in the placebo group. Of 316 patients who received CT at 28 days, stone passage occurred in 140 of 161 (87.0%) in the tamsulosin group and 127 of 155 (81.9%) with placebo, a difference of 5.0% (95% confidence interval -3.0% to 13.0%). In a prespecified subgroup analysis of large stones (5 to 10 mm), 30 of 36 (83.3%) tamsulosin participants had stone passage compared with 25 of 41 (61.0%) with placebo, a difference of 22.4% (95% confidence interval 3.1% to 41.6%) and number needed to treat of 4.5. There was no difference in urologic interventions, time to self-reported stone passage, pain, or analgesia requirements. Adverse events were generally mild and did not differ between groups.

Conclusion: We found no benefit overall of 0.4 mg of tamsulosin daily for patients with distal ureteric calculi less than or equal to 10 mm in terms of spontaneous passage, time to stone passage, pain, or analgesia requirements. In the subgroup with large stones (5 to 10 mm), tamsulosin did increase passage and should be considered. [Ann Emerg Med. 2016;67:86-95.]

Please see page 87 for the Editor's Capsule Summary of this article.

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0196-0644/\$-see front matter

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<http://dx.doi.org/10.1016/j.annemergmed.2015.06.001>

INTRODUCTION

Background

Ureteric calculi are a common reason for presenting to the emergency department (ED), with more than a million ED visits per year in the United States.¹ Ureteric calculi are estimated to affect up to 12% of men and 6% of women in their lifetime² and typically affect young and healthy adults. There are limited data on spontaneous passage rates of ureteric calculi, but factors such as stone size, location, smooth muscle spasm, edema, and anatomy are known to affect passage.^{3,4} Calculi greater than 5 mm in diameter frequently require intervention.⁵ A number of pharmacologic agents have been used to facilitate stone passage, so-called medical expulsive therapy. The most frequently recommended agents are α -blockers, specifically tamsulosin. Commonly used for benign prostatic hypertrophy,

tamsulosin acts at the α -1D adrenergic receptors present in the distal ureter. Guidelines suggest it may be appropriate to offer medical therapy as part of a strategy of observation and periodic evaluation for newly diagnosed stones less than 10 mm in diameter; however, these recommendations are based on limited and poor-quality data and come with the caveat that they be administered "off label."³

Importance

Numerous published clinical trials of tamsulosin have been limited by small size and serious methodological issues such as lack of blinding, no placebo, use of adjunctive medications, and poorly defined primary outcomes of stone passage, all of which call into question the validity of the results.⁶⁻²³ A recent systematic review of α -blockers²⁴ demonstrated a high risk of bias overall in the studies

Editor's Capsule Summary

What is already known on this topic

Tamsulosin has been suggested to enhance passage of ureteral stones (“medical expulsive therapy”), but most previous studies have been methodologically flawed.

What question this study addressed

Does tamsulosin enhance overall passage of symptomatic distal ureteral stones in emergency department patients? Is stone size a factor?

What this study adds to our knowledge

In 316 patients with symptomatic stones and 28-day computed tomography follow-up, the rate of stone passage was similar between tamsulosin and placebo. In the 103 patients with 5- to 10-mm stones, however, the stone passed more frequently with tamsulosin.

How this is relevant to clinical practice

In symptomatic patients with 5- to 10-mm stones whose size and location are known, tamsulosin increases the likelihood of stone passage and might in some cases preclude the need for urologic intervention.

conducted to date, with only 7 of 32 studies describing any blinding of participants and investigators, and significant clinical and statistical heterogeneity. Although the authors concluded that there is sufficient evidence to recommend α -blockers for medical expulsive therapy, they conceded the methodological limitations of the studies and recommended further placebo-controlled trials to draw final conclusions. Furthermore, the external validity of trials conducted with outpatients in a urology setting compared with individuals managed in the ED could also be questioned. The relative benefits and harms of medical expulsive therapy in ED patients with ureteric colic remain unknown, and consequently use of this therapy has been sporadic.

Goal of This Investigation

The objective of this study was to assess the efficacy of tamsulosin 0.4 mg orally daily for 28 days compared with placebo in the management of patients with distal ureteric stones less than or equal to 10 mm in diameter and being discharged home from the ED with prespecified subgroups of stones less than 5 mm and 5 to 10 mm.

MATERIALS AND METHODS

Study Design and Setting

A multicenter, randomized, double-blind, placebo-controlled trial was conducted in 5 EDs (4 tertiary and 1 regional district) in Queensland, Australia, with a combined annual census of more than 300,000. Three of the departments, The Townsville Hospital, Gold Coast University Hospital, and Robina Hospital, are mixed (adult and pediatric) departments, whereas the Royal Brisbane and Women's Hospital and Princess Alexandra Hospital are predominantly adult departments. Urologic services were available on site at the 4 tertiary hospitals. The study was approved by the human research and ethics committees of participating hospitals and universities. The trial was prospectively registered with the Australian New Zealand Clinical Trial Registry. Patient recruitment commenced in October 2010 and finished in March 2014.

Selection of Participants

Patients were eligible for inclusion if they were older than 18 years and with symptoms suggestive of ureteric colic and a calculus demonstrated in the distal ureter on computed tomography (CT) scan with a CT kidneys, ureter, and bladder protocol. The distal ureter was defined as distal to the sacroiliac joint on CT, and size was defined as the largest diameter in 3 planes. Stone location and size were determined by the reporting radiologist. Participants were excluded if they had a temperature greater than 38°C (100.4° F), an estimated glomerular filtration rate less than 60 mL/minute per 1.73 m², a calculus greater than 10 mm, solitary kidney, transplanted kidney, history of ureteral stricture, known allergic reaction to the study medication, or current calcium channel blocker or α -blocker use or hypotension (systolic blood pressure <100 mm Hg), or if they were pregnant or planning pregnancy. Participants were identified in the ED by clinical medical staff and written informed consent was obtained by a member of the study team, a research assistant, or a member of the medical staff not directly responsible for patient care. Baseline information was collected and recorded on case report forms. Screening logs of potentially eligible patients were augmented with identification of potentially eligible patients on ED databases.

Interventions

The tamsulosin and identical placebo were provided by the manufacturer (CSL Biotherapies, Parkville, Victoria, Australia). Sequentially numbered study packs were securely stored at the study sites. The randomization sequence was produced with a computer-generated program in permuted blocks of random lengths stratified by hospital and stone

size (“small” and “large” stones being <5 mm and 5 to 10 mm, respectively). The sequence was generated by a clinical trial pharmacist not otherwise involved in the study and was securely stored and known only to the trial pharmacist.

Each study medication pack contained either tamsulosin 0.4 mg or placebo. Once informed consent was obtained and patients were deemed appropriate for discharge, they were allocated to the next sequentially numbered study medication pack. Patients were instructed to receive the study medication daily for 28 days or until definite stone passage (ie, evidence of stone on urine straining). Analgesia was at the discretion of the treating physician; however, the recommended regimen was indomethacin 25 to 50 mg 3 times daily orally (unless contraindicated) and oxycodone 5 to 10 mg 3 times a day as required for breakthrough. Investigators, the treating physician, and patients were blinded to the allocation for the duration of the study and data analysis.

Methods of Measurement

Participants were asked to record symptoms in a “patient diary” provided on discharge to assist with recall of symptoms. Participants were contacted by telephone for a structured interview at 7, 14, 21, and 28 days by research staff. Pain was recorded as the number of pain episodes, the worst pain score during a 24-hour period with a verbal numeric pain scale, or whether they were currently pain free. The verbal numeric pain scale (0 to 10) has been validated for use in ED research and found to correlate well with the more commonly used visual analog scale.²⁵ The minimum clinically significant difference in pain is accepted to be 1.3 points.²⁶ Participants were asked whether they had experienced any adverse effects, including prompts for commonly reported adverse effects (dizziness, palpitations, collapse/blackouts, sexual dysfunction, headaches, fatigue, nausea, vomiting, diarrhea, and constipation). At 28-day follow-up, limited pelvic noncontrast CT was performed to determine stone passage. All CTs were reported by consultant radiologists who were blinded to group allocation. Compliance was based on self-report by participants. Additionally, to assess the success of blinding they were asked at the completion of the study whether they thought that they had received the active or the placebo medication. Research staff collated data from the patients and from hospital databases. Data were entered into a computer database designed for the trial with inbuilt logic and range checks.

Outcome Measures

The coprimary outcomes were stone expulsion and time to stone expulsion. Stone expulsion was defined as absence of stone on repeated, noncontrast, limited pelvic CT at

28 days. Time to stone expulsion in days was defined as self-reported definitive passage of the calculus or first day of a pain-free 48-hour period, with calculus absent on repeated CT. Secondary outcomes included unplanned re-presentations to the ED or hospital admission, total analgesia requirements, pain scores measured on the verbal numeric pain scale, need for urologic intervention, complications including infection (defined as positive culture result for pathogenic bacteria in blood or urine), renal impairment (defined as decrease in estimated glomerular filtration rate of at least 20 mL/minute per 1.73 m²), days off work (as reported by patients), and adverse effects from study drugs.

Primary Data Analysis

The sample size calculation was based on improving passage for stones 5 to 10 mm in diameter. Limited data were available for accurate estimates of stone passage in this group, with some studies indicating spontaneous passage of large stones to be unlikely^{5,27}; however, we determined that 49 patients per group would be required to increase stone passage from 5% to 25%, according to an α of .05 and a power of 0.8. We aimed to collect data in both groups until a total of 100 stones greater than or equal to 5 mm had been included. In accordance with existing hospital data, we anticipated approximately 4 small stones (<5 mm) for each large one (5 to 10 mm).

Data were analyzed with Stata (version 12; StataCorp, College Station, TX). Primary analyses were performed following the intention-to-treat principle. Statistical significance was set at $\alpha < .05$. An investigator blinded to the study group assignments performed the analyses.

Descriptive statistics were used to describe the baseline characteristics of the study population. The proportion of patients with stone passage at 28 days was calculated for each treatment group, and the difference between the group proportions and 95% confidence interval (CI) of the difference was reported. A preplanned subgroup comparison of the difference in stone passage for small and large stones also was performed with the same approach. Kaplan-Meier analysis was used to examine time to stone expulsion, and log-rank analyses were used to compare treatment groups.

For secondary outcomes, categorical variables were described with the number and percentage of individuals within each group. The difference between percentages in each treatment group and the 95% CI of the difference were reported and *P* values were generated from the χ^2 test. Continuous outcomes were described with the median (interquartile range) because all were positively skewed. The difference between medians and the Bonnett-Price 95% CI of the difference were calculated and *P* values were

generated with a Mann-Whitney *U* test. Categorical variables included unplanned re-presentation to the ED, hospital admission, urologic intervention, positive urine culture result, renal impairment, and adverse effects from study drugs. Continuous outcomes included analgesia requirements, days off work, total number of pain episodes during 28 days, and worst pain scores during the 28 days. The median number of days off work was 0 in each group. As such, the mean was also reported and robust Poisson standard errors were used to estimate the CI for the difference between means. The majority of individuals reported pain scores of 0 at 14-, 21-, and 28-day follow-up. The proportion of patients in each treatment group with a pain score greater than 0 was calculated at each of the times.

Because there were patients with missing data on the outcome variable, sensitivity analyses were conducted. Such analyses included missing data under the following scenarios: best case, in which all patients with missing data passed their stones; worst case, in which no patients with missing data passed their stones; and control group, in which stone passage rate for patients with missing data was set to the stone passage rate in the control group. Additional sensitivity analyses examined treatment failure across treatment groups, with treatment failure defined as stone presence on CT or urologic intervention, and the effect of stone location on stone passage by reporting the proportion of patients with stone passage by stone location and treatment group.

RESULTS

Characteristics of Study Subjects

We enrolled 403 individuals in the trial; 202 were allocated to tamsulosin and 201 to placebo. Three patients were excluded from the analysis (1 in the tamsulosin group and 2 in the placebo group) because they did not have a stone reported on initial CT. An additional 7 participants were removed from the analysis (3 in the tamsulosin and 4 in the placebo group) because they did not have a distal stone. This left 393 patients in the analysis, 198 allocated to tamsulosin and 195 allocated to placebo. Six patients were enrolled in the trial and had an estimated glomerular filtration rate less than 60 mL/minute per 1.73 m², 5 in the tamsulosin group and 1 in the placebo group. These patients were retained in the analysis. Participant flow is summarized in Figure 1. Demographic characteristics were similar across treatment groups (Table 1).

Main Results

There were 161 patients (81.3%) in the tamsulosin group and 155 (79.5%) in the placebo group who received

a follow-up CT. Stone passage occurred in 140 (87.0%) of the tamsulosin patients and 127 (81.9%) of the placebo patients. This was a nonsignificant difference of 5.0% (95% CI -3.0% to 13.0%; *P*=.22). Of the patients with large stones, 77 had a follow-up CT, 36 in the tamsulosin group and 41 in the placebo group. Spontaneous stone passage occurred for 30 patients (83.3%) in the tamsulosin group and 25 (61.0%) in placebo group. The difference between groups was 22.4% (95% CI 3.1% to 41.6%; *P*=.03), with a number needed to treat of 4.5. Of the patients with small stones, 239 had a follow-up CT, 125 in the tamsulosin group and 114 in the placebo group. Spontaneous stone passage occurred for 110 patients (88.0%) in the tamsulosin group and 102 (89.5%) in the placebo group, a difference of -1.5% (95% CI -9.5% to 6.5%; *P*=.72). Table 2 summarizes the data for the primary outcome. Combining urologic intervention and stone remaining on CT as treatment failure demonstrated similar results (Appendix E1, available online at <http://www.annemergmed.com>).

There were 377 patients with evaluable data on time to stone passage, 189 in the tamsulosin group, and 188 in the placebo group. Within 28 days, 148 patients in the tamsulosin group and 135 in the placebo group reported spontaneous stone passage. An additional 10 patients in the tamsulosin group and 15 in the placebo group were censored before 28 days as a result of loss to follow-up. The median time to stone passage was 7 days for tamsulosin (95% CI 5 to 10 days) and 11 days for placebo (95% CI 6 to 14 days). The time to stone passage functions did not differ across treatment groups (log-rank $\chi^2=2.8$; *P*=.10) (Figure 2).

The tamsulosin and placebo groups did not differ in terms of the proportion of patients who had greater than or equal to 1 ED re-presentation, greater than or equal to 1 hospital admission, or a urologic intervention (Table 3). With regard to analgesia use, total number of 5-mg oxycodone tablets and total number of 25-mg indomethacin tablets was similar in each group (Table 3). The majority of pain relief was received during the first week (Figure E1, available online at <http://www.annemergmed.com>).

The median number of pain episodes reported was 4 in both groups (Figure 3 and Table 3). Similarly, the median worst pain score was 5 in both groups. The proportion of patients with a worst pain score greater than 0 at 7, 14, 21, and 28 days did not differ across groups, with the majority of patients being pain free by 14-day follow-up (Table 3). There were no differences between groups in incidence of positive urine culture result (1 in each group) or renal impairment (6 in each group).

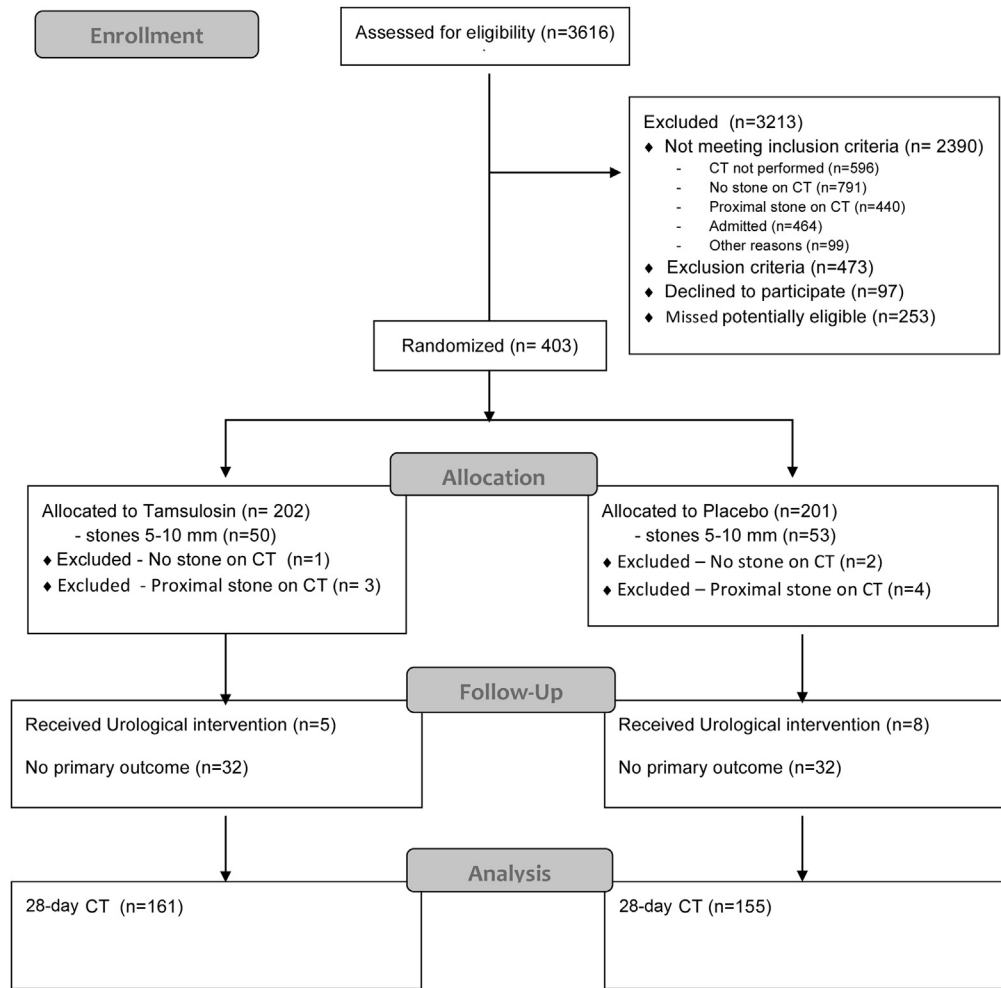


Figure 1. CONSORT flow diagram.

Adverse events were frequently reported; however, there was no significant difference between treatment groups. These are summarized in Table 4. Self-reported compliance was poor in both treatment groups. One hundred nine of

Table 1. Baseline characteristics of the study sample.

Characteristic	Tamsulosin (n=198)	Placebo (n=195)
Median (IQR) age, y	45.5 (35–55)	46 (37–55)
Men, No. (%)	156 (78.8)	164 (84.1)
Median (IQR) stone size, mm	4.0 (3–5)	3.7 (3–5)
Stone 5–10 mm, No. (%)	50 (25.3)	53 (27.2)
Left-sided stone, No. (%)	106 (53.5)	90 (46.2)
Vesicoureteric junction stone, No. (%)	123 (62.1)	129 (66.2)
eGFR <90 mL/min per 1.73 m ² , No. (%)	119 (60.1)	133 (68.2)
Urine culture performed, No. (%)	137 (69.2)	120 (61.5)
Negative urine culture result, No. (% of urine cultures)	118 (86.1)	99 (82.5)
Contaminated urine culture, No. (% of urine cultures)	15 (10.9)	16 (13.3)
Positive urine culture result, No. (% of urine cultures)	4 (2.9)	5 (4.2)

IQR, Interquartile range; eGFR, estimated glomerular filtration rate.

169 patients (64.5%) in the tamsulosin group and 112 of 174 (64.4%) in the placebo group reported receiving 1 tablet per day for 28 days, a difference of 0.1% (95% CI –10.0% to 10.3%). Of patients with available follow-up data, approximately one fifth reported being less than fully compliant at day 7 (21.9% for tamsulosin versus 21.0% for placebo). This increased to approximately one quarter at 14 days (26.4% for tamsulosin versus 26.4% for placebo), 21 days (26.9% for tamsulosin versus 27.6% for placebo), and 28 days (28.6% for tamsulosin versus 30.2% for placebo). Blinding of participants was assessed as being successful, with participants unable to correctly identify their allocation (Appendix E2, available online at <http://www.annemergmed.com>).

Sensitivity Analyses

Sensitivity analysis testing the effect of various assumptions to account for missing data and stone location on passage is reported in Appendix E3, available online at <http://www.annemergmed.com>. Patients with missing

Table 2. Patient outcomes by treatment group.

Endpoint	Tamsulosin	Placebo	% Difference (95% CI)
All patients	(n=198)	(n=195)	
No follow-up CT or intervention	32 (16.2)	32 (16.4)	-0.2 (-7.6 to 7.1)
Urologic intervention*	5 (2.5)	8 (4.1)	-1.6 (-5.1 to 2.0)
Follow-up CT	161 (81.3)	155 (79.5)	1.8 (-6.0 to 9.7)
Stone passage on CT, No. (%)	140 (87.0)	127 (81.9)	5.0 (-3.0 to 13.0)
Small stones (<5 mm)	(n=148)	(n=142)	
No follow-up CT or intervention	22 (14.9)	24 (16.9)	-2.0 (-10.5 to 6.4)
Urologic intervention	1 (0.7)	4 (2.8)	-2.1 (-5.2 to 0.9)
Follow-up CT	125 (84.5)	114 (80.3)	4.2 (-4.6 to 12.9)
Stone passage on CT, No. (%)	110 (88.0)	102 (89.5)	-1.5 (-9.5 to 6.5)
Large stones (5–10 mm)	(n=50)	(n=53)	
No follow-up CT or intervention	10 (20.0)	8 (15.1)	-4.9 (-9.8 to 19.6)
Urologic intervention	4 (8.0)	4 (7.6)	-0.5 (-9.9 to 10.8)
Follow-up CT or intervention	36 (72.0)	41 (77.4)	-5.3 (-22.1 to 11.4)
Stone passage on CT, No. (%)	30 (83.3)	25 (61.0)	22.4 (3.1 to 41.6)

*Patients undergoing urologic intervention did not have a CT performed at 28 days.

outcome data were slightly younger (41.3 versus 46.2 years; difference -4.8 years; 95% CI -8.2 to -1.5 years) but otherwise similar to those with complete outcome data. Scenarios for missing data did not change results substantially.

LIMITATIONS

There are a number of important limitations. First, the possibility of some selection bias cannot be excluded. Recruitment into ED trials by busy staff with competing

priorities is challenging. Screening logs maintained at the hospital sites were augmented by searching ED databases for potentially eligible patients, so we believe we have accurate estimates of their numbers. Although recruitment was slower than anticipated, we do not believe that any systematic bias was introduced.

We anticipated approximately 4 small stones for every large stone, but the observed rate of small stones was less. The trial, however, was primarily designed to have adequate power to detect a difference in the large-stone group.

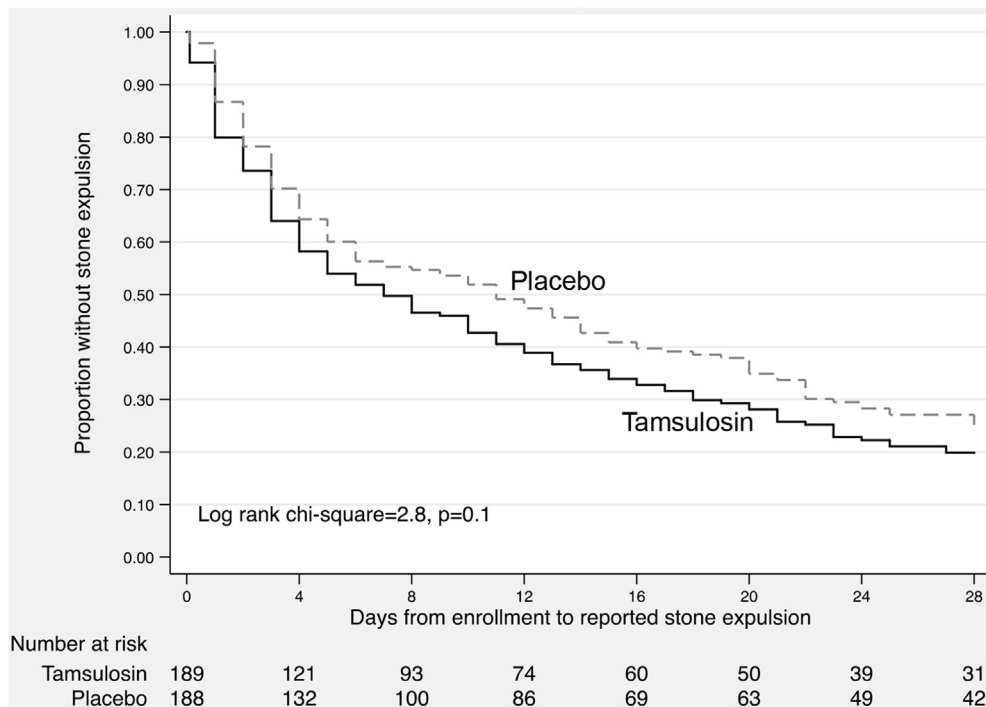


Figure 2. Time to stone passage.

Table 3. Secondary endpoints by treatment group.*

Outcome	Tamsulosin	Placebo	Difference (95% CI of the Difference)	P
Health care use	(n=198)	(n=195)		
≥1 re-presentation to ED within 28 days	31 (15.7)	35 (18.0)	-2.3 (-9.7 to 5.1)	.54
≥1 admission to the hospital within 28 days	20 (10.1)	23 (11.8)	-1.7 (-7.9 to 4.5)	.59
Urologic intervention	5 (2.5)	8 (4.1)	-1.6 (-5.1 to 2.0)	.38
Analgesia	n=164	n=168		
Median (IQR) 5 mg oxycodone	0 (0 to 5.5)	0 (0 to 3.5)	0 (-0.7 to 0.7)	.36
Median (IQR) 25 mg indomethacin	0 (0 to 3)	0 (0 to 3)	0 (0 to 0)	.67
Pain data				
Median (IQR) pain episodes during 28 days (n=335)	4 (1 to 10)	4 (1 to 12)	0 (-1.7 to 1.7)	.32
Median (IQR) worst pain score (n=367)	5 (1 to 8)	6 (2 to 8)	-1 (-2.1 to 0.9)	.12
Pain score >0 at 7 days (n=367)	142 (76.8)	143 (78.6)	-1.8 (-10.3 to 6.7)	.68
Pain score >0 at 14 days, (n=353)	60 (34.1)	58 (32.8)	1.3 (-8.5 to 11.2)	.79
Pain score >0 at 21 days (n=343)	34 (20.0)	37 (21.4)	-1.4 (-10.0 to 7.2)	.75
Pain score >0 at 28 days (n=347)	26 (15.0)	28 (16.1)	-1.1 (-8.7 to 6.6)	.79
Complications	n=164	n=165		
Median (IQR) days unable to attend work	0 (0 to 2)	0 (0 to 2)	0 (-0.7 to 0.7)	.80
Mean (SD) days off work per person	1.5 (2.7)	1.4 (2.19)	0.1 (-0.27 to 0.55)	.50

*Data are presented as No. (%) unless otherwise indicated.

The primary outcome was stone passage on CT at 28 days. Although this overcame the limitation of previous work with self-reported (or physician-assessed) stone passage, we did not obtain a follow-up CT for approximately 17% of participants in both groups. The time frame of 28 days for follow-up CT was chosen to allow maximum time for spontaneous passage to occur; however, the majority of patients at this point did not have ongoing symptoms,

so perhaps the reluctance to attend this appointment is understandable. Patients with missing outcome data were slightly younger but otherwise similar to patients with complete data. Sensitivity analysis of various scenarios about missing data did not alter the results; however, we cannot exclude the possibility of some bias caused by attrition.

Compliance was also problematic. Five patients in the trial reported not receiving any trial medications, and

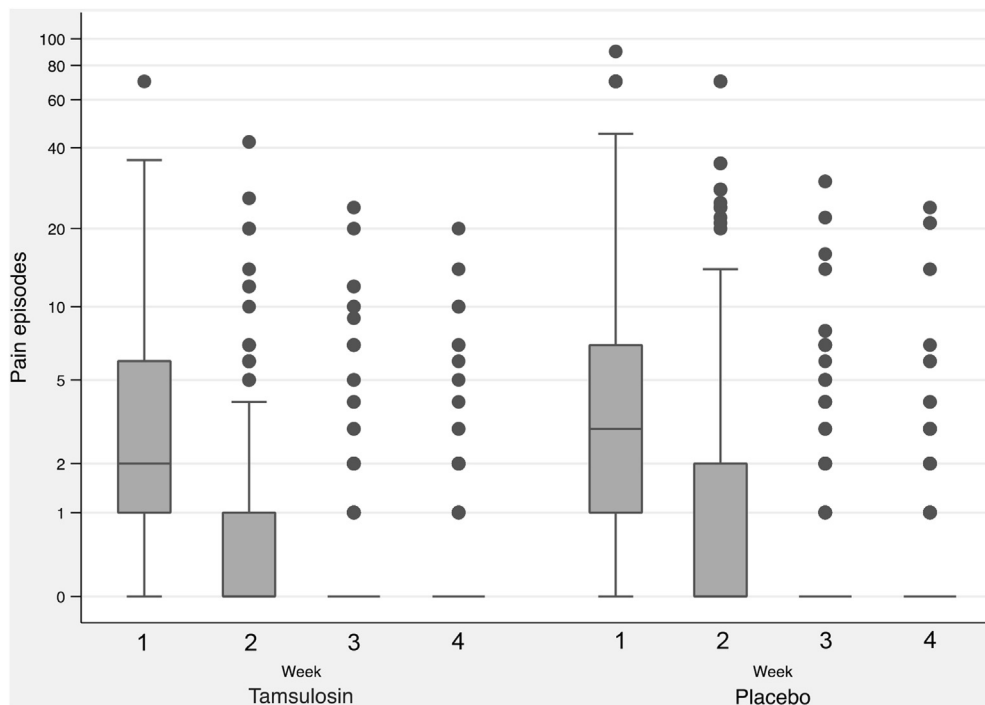


Figure 3. Number of pain episodes per week.

Table 4. Adverse events by treatment group.*

Adverse Event	Day 7 Follow-up			At Any Time During 28 Days for Patients With Complete Follow-up		
	Tamsulosin (n=185)	Placebo (n=185)	Difference (95% CI)	Tamsulosin (n=169)	Placebo (n=173)	Difference (95% CI)
Dizziness	41 (22.2)	35 (18.9)	3.2 (-5.0 to 11.5)	46 (27.2)	36 (20.8)	6.4 (-2.6 to 15.4)
Palpitations	11 (6.0)	9 (4.9)	1.1 (-3.5 to 5.7)	13 (7.7)	14 (8.1)	-0.4 (-6.1 to 5.3)
Collapse	0	2 (1.1)	-1.1 (-2.6 to 0.4)	3 (1.8)	2 (1.2)	0.6 (-1.9 to 3.2)
Sexual dysfunction	10 (5.4)	4 (2.2)	3.2 (-0.6 to 7.1)	13 (7.7)	5 (2.9)	4.8 (-0.1 to 9.5)
Headache	40 (21.6)	54 (29.2)	-7.6 (-16.4 to 1.3)	50 (29.6)	56 (32.4)	-2.8 (-12.6 to 7.0)
Fatigue	53 (28.7)	44 (23.8)	4.9 (-4.1 to 13.8)	55 (32.5)	47 (27.2)	5.4 (-4.3 to 15.1)
Nausea	56 (30.3)	56 (30.3)	0 (-9.4 to 9.4)	53 (31.4)	55 (31.8)	-0.4 (-10.3 to 9.4)
Vomiting	17 (9.2)	19 (10.3)	-1.1 (-7.1 to 5.0)	14 (8.3)	18 (10.4)	-2.1 (-8.3 to 4.0)
Diarrhea	19 (10.3)	19 (10.3)	0.0 (-6.2 to 6.2)	23 (13.6)	22 (12.7)	0.9 (-6.3 to 8.1)
Constipation	33 (17.8)	32 (17.3)	0.5 (-7.2 to 8.3)	36 (21.3)	28 (16.2)	5.1 (-3.1 to 13.4)

*Data are presented as No. (%).

compliance was generally poor in both groups. Our definition of compliance was stringent, and compliance was similar in both groups. The intention-to-treat analysis would minimize bias associated with this aspect. Given the poor compliance to the treatment regimen under trial conditions, we believe that compliance is likely to be an issue in actual practice too. In some respects, the trial results could be considered pragmatic in assessing the effectiveness of the intervention.

The trial, although multicenter, was conducted in a single state in Australia. The results may not be applicable to other populations. Measurement bias and recall bias may have limited the utility of pain and analgesia requirement data, but it is likely to have affected both groups equally. Adverse events were frequently reported in both groups. It is possible adverse events were attributable to the underlying condition or coadministered drugs rather than the intervention under investigation.

DISCUSSION

To our knowledge, this study is the largest clinical trial evaluating tamsulosin versus placebo in distal ureteric calculi. We found that treatment with tamsulosin did not affect stone passage overall. There was an apparent trend to benefit, which can be explained by a beneficial treatment effect in patients with large stones (≥ 5 mm), a prespecified subgroup. Stone passage in patients with small stones (< 5 mm) was almost identical in both groups. There was no difference between groups for the clinically important outcome of need for urologic intervention, either overall or in the large stone subgroup.

A 2014 Cochrane review on medical expulsive therapy with α -blockers concluded that they resulted in higher stone-free rates and a shorter time to stone expulsion.²⁴ Tamsulosin was the most commonly evaluated agent and

was a major contributor to conclusions about the overall treatment effect. However, the review included many heterogeneous trials and cointerventions in comparator groups such as aescin (an antiedema extract from the horse chestnut tree) and steroids that are not considered routine care in many settings. The authors conceded that the majority of trials included only a small number of patients and had variable methodological quality, which may call into question the validity of the results.²⁸ Of previous trials evaluating tamsulosin, only 5 could be considered at low risk of bias overall.²⁹⁻³³ The results of these all demonstrated conflicting results, but closer examination demonstrated concordance with results of our trial, with benefit in larger stones and lack of benefit in smaller ones. Stones in trials by Abdel-Meguid et al²⁹ (n=150) and Al Ansari et al³⁰ (n=96) were an average of 5 to 6 mm in diameter and demonstrated benefit with expulsion rates of 81% and 82%, respectively, with tamsulosin compared with 56% and 61%, respectively, with placebo. These differences were statistically significant. Trials by Vincendeau et al³³ (n=129) and Hermanns et al³² (n=100) included average stone sizes of 3 to 4 mm and had stone expulsion rates of 77% and 87%, respectively, with tamsulosin compared with 71% and 89%, respectively, with placebo, which were not significant. A study by Ferre et al³¹ (n=90) was one of the few studies conducted in the ED setting. The mean stone size in this study was 3.6 mm, and no demonstrated benefit was observed with stone expulsion in 77% of the tamsulosin group compared with 65% in the standard care group ($P=.50$).

We did not find a difference between groups in time to stone passage with Kaplan-Meier analysis. When this outcome has been previously reported, it has tended to favor tamsulosin.²⁴ We found self-reported stone passage to be an unreliable method of determining definite stone passage, with only approximately a third of patients

reporting definite stone passage, with similar low rates reported previously.³⁴ Some of the inconsistency with previous trials may be attributed to their methods, which may have resulted in substantial bias. We did not find a significant difference in pain or analgesia requirements.

We observed spontaneous passage rates of large stones in our control group that were higher than anticipated and higher than previously reported in observational data.³ This is similar to more recent trial data.^{29,30}

There was no difference in reported adverse effects. There were no serious adverse effects in either group, and reported effects were generally mild and self-limiting. Previous reports have generally reported higher adverse effects with tamsulosin. The high rate of reported effects in the placebo group suggests that this may have been due to a placebo effect, the effect of the underlying condition, or coadministered medications.

In summary, this study found no benefit overall of 0.4 mg of tamsulosin daily as medical expulsive therapy for patients with distal ureteric calculi less than or equal to 10 mm in terms of spontaneous passage, time to stone passage, pain, or analgesia requirements. The intervention was generally well tolerated, and adverse effects were similar in both groups, although compliance was generally poor. The prespecified subgroup of patients with large stones of 5 to 10 mm did have increased rates of spontaneous passage with the addition of tamsulosin, which should therefore be recommended if no contraindications exist. Because spontaneous passage is very likely with patients with stones less than 5 mm and we found no benefit from the intervention, a strategy of observation and periodic reevaluation should be used for this group.

The authors thank Sarah Cochrane, BNSc, Leonie Jones, MHS, Kelvin Robertson, MCLinTRes, Tracey Hawkins, BNSc, Chris Heenan, and Rob Eley, PhD, for assistance in conducting the trial at their sites, and Tanya Gray, PhD in assistance with protocol development and obtaining funding. They also thank the participants and all other staff at participating hospitals who contributed.

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Author contributions: JSF, KC, and JG conceived the study, designed the trial, and obtained research funding. JSF, KC, CB, GK, OT, TT, and CD supervised the conduct of the trial and data collection, undertook recruitment of participants, and managed the data, including quality control. JG provided statistical advice on study design and analyzed the data. JSF drafted the article, and all authors contributed substantially to its revision. JSF had full access to all the study data and final responsibility for the decision to submit for publication. JSF takes responsibility for the paper as a whole.

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 as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist and provided the following details: Supported by a grant from the Queensland Emergency Medicine Research Foundation.

Publication dates: Received for publication March 31, 2015. Revision received May 19, 2015. Accepted for publication May 29, 2015. Available online July 17, 2015.

Presented at the Australasian College for Emergency Medicine annual scientific meeting, Melbourne, Victoria, Australia, December 2014.

Clinical trial registration number: ACTRN12610000623099

CSL Biotherapies had no involvement in study initiation, design, data collection, data analysis, data interpretation, or article writing.

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APPENDIX E1.**Treatment failure**

There were 329 patients (166 in the tamsulosin group and 163 in the placebo group) who either had a 28-day CT or a urologic intervention within 28 days. Treatment failure, defined as stone remaining on CT or urologic intervention, occurred in 26 patients (15.7%) in the tamsulosin group and 36 (22.1%) in the placebo group. This was a nonsignificant difference of -6.4% (95% CI -14.9% to 2.0% ; $P=.14$).

For the small-stone group, there were 126 patients in the tamsulosin group and 118 in the placebo group with a stone remaining on CT or a urologic intervention. Treatment failure occurred in 16 patients (12.7%) in the tamsulosin group and 16 (13.6%) in the placebo group, a difference of -0.9% (95% CI -9.3% to 7.6% ; $P=.84$). For the large-stone group, there were 40 in the tamsulosin group and 45 in the placebo group with a stone remaining on CT or a urologic intervention. Treatment failure occurred in 10 patients (25%) in the tamsulosin group and 20 (44.4%) in the placebo group. This was a difference of -19.4% (95% CI -39.2% to 0.3% ; $P=.06$).

APPENDIX E2.**Blinding success**

There were available data for 169 patients in the tamsulosin group and 167 in the placebo group. There was no significant difference in perceptions across the 2 groups ($P=.55$). There were 34 (20.12%) and 29 (17.37%) patients in the tamsulosin and placebo groups, respectively, who thought they were receiving placebo. There were 52 (30.77%) and 46 (27.54%) patients in the tamsulosin and placebo groups, respectively, who thought they were receiving active medication, and 83 (49.11%) and 92 (55.09%) patients in the tamsulosin and placebo groups, respectively, who said they were not sure what group they were in.

APPENDIX E3.**Sensitivity analysis**

There were 32 patients (16.2%) in the tamsulosin group and 32 (16.4%) in the placebo group who did not receive a 28-day CT scan or have a urologic intervention. Patients with missing outcome data were slightly lower median age (37.5 versus 47.0 years; difference -9.5 years; 95% CI of difference -13.67 to -5.33 years). Similar proportions of patients with missing and nonmissing outcome data

were men (84.4% versus 80.9%; difference 3.5%; 95% CI -6.3% to 13.4%), and had vesico-ureteric junction stones (67.2% versus 63.5%; difference 3.7%; 95% CI -8.9% to 16.3%). Median stone size was similar for patients with and without missing data (3.5 versus 4 mm; difference 0.5 mm; 95% CI -1.02 to 0.02 mm). Patients with missing data were less likely to be compliant. For example, of those with 7-day follow-up data, 26 of 51 patients (51.0%) with missing outcome data were not compliant, whereas 54 of 322 patients (16.8%) with data were not compliant (difference 34.2%; 95% CI 19.9% to 48.5%).

A best-case sensitivity analysis was conducted in which it was assumed that all patients with missing data had passed their stones. Patients with a urologic intervention were not included in any of the sensitivity analyses. Under this scenario, 172 of 193 patients (89.1%) in the tamsulosin group and 159 of 187 (85.03%) in the placebo group would have passed their stones, a difference between groups of 4.1% (95% CI -2.6% to 10.8%). Assuming the worst-case scenario in which it was assumed that none of the patients had passed their stones, 140 of 193 tamsulosin subjects (72.5%) and 127 of 187 placebo subjects (67.9%) would have passed their stones, a difference of 4.6% (95% CI -4.6% to 13.8%). Under a scenario in which patients with missing data had an expulsion rate equivalent to that of the placebo group (81.9%), 26 of the 32 patients with missing data would be assumed to have passed their stones. This is equivalent to 166 of 193 patients (86.0%) in the tamsulosin group and 153 of 187 (81.8%) in the placebo group, a difference between groups of 4.2% (95% CI -3.2% to 11.6%). Sensitivity analysis for large stones, under a best-case scenario, did not change results, with passage rates of 40 of 46 (86.96%) in the tamsulosin group and 33 of 49 (67.35%) in placebo group (difference 19.61; 95% CI 3.27 to 35.95; $P=.02$).

An additional analysis was conducted to determine the effect of stone location on passage. Stone passage was more likely with vesicoureteric stones (182/203; 89.7%) than for more proximal distal stones (85/113; 75.2%), a difference of 14.4% (95% CI 5.4% to 23.4%). Stone passage was higher in the tamsulosin group (93/97; 95.9%) than the placebo group (89/106; 84.0%) for vesicoureteric stones, a difference of 11.9% (95% CI 3.9% to 19.9%). For more proximal stones, stone passage was similar in the tamsulosin (47/64; 73.4%) and placebo (38/49; 77.6%) groups, with a difference of -4.1% (95% CI -20.0% to 11.8%).

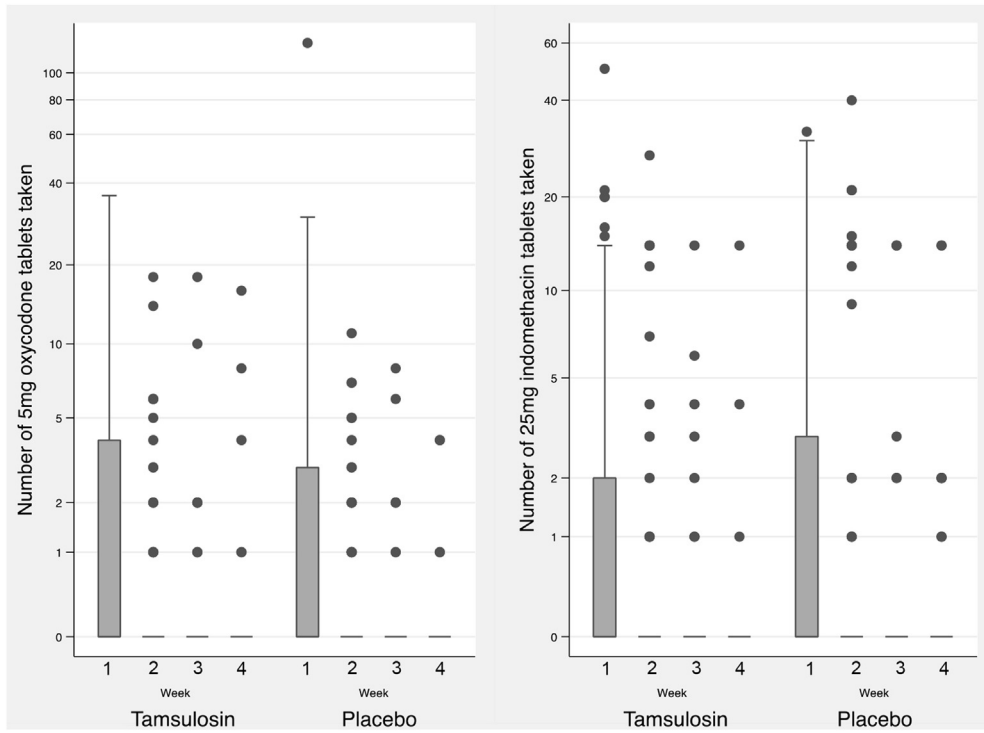


Figure E1. Number of analgesia medication tablets received per week.