Critical Review Form
Therapy

Vincendeau S, Bellissant E, Houlgatte A, Doré B, Bruyère F, Renault A, Mouchel C, Bensalah K, Guillé F; Tamsulosin Study Group. Tamsulosin hydrochloride vs placebo for management of distal ureteral stones: a multicentric, randomized, double-blind trial. Arch Intern Med. 2010 Dec 13;170(22):2021-7.

Objectives: **"to evaluate the efficacy and safety of tamsulosin, 0.4 mg/d, in patients with acute renal colic owing to a small distal ureteral stone." (p. 2022)**

Methods: **This prospective, multicenter, placebo-controlled, randomized trial was conducted at 6 French emergency departments from February 1, 2002 to December 6, 2006. One of the six centers (which had only enrolled 2 patients) was excluded due to clinical practice deficiencies). Patients older than 18 years of age with a radiopaque distal ureteral stone between 2 and 7 mm in diameter were eligible for inclusion. Exclusion criteria were pregnancy, breastfeeding, concomitant use of alpha or beta-blockers, transient hypotension, liver impairment, the need for a surgical procedure either due to infection or continued pain after medical treatment, or spontaneous passage of the stone prior to randomization.**

Enrolled patients were admitted to the urology service and treated with oral ketoprofen and phloroglucinol for 5 days, along with either tamsulosin (0.4 mg) or placebo until stone expulsion or day 42, whichever came first. Patients were discharged when they reported no pain. All patients were followed-up at day 7 and every 7 days thereafter until day 42. All patients underwent plain radiography at each follow-up visit (except days 21 and 35).

The primary endpoint was time to stone expulsion. Multiple secondary endpoints were evaluated, including rates of stone expulsion at each visit, need for surgical intervention, pain relapse and time to pain relapse, and adverse effects.

A total of 129 patients were enrolled, of whom 2 were excluded due to exclusion of the recruiting center. Another 5 patients were excluded (1 in the placebo group for major deviation from the inclusion criteria; 3 in the treatment group for major deviation from the inclusion criteria and 1 for consent withdrawal). This left 122 patients in the final analysis with 61 patients in each group. The mean age was 38.9 years and 77.9% were male.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	Yes. “Randomization was performed, concealed, and stratified by center in blocks of 4 according to a computer-generated random number table.” (p. 2022)
2.	Was randomization concealed (blinded)? In other words, was it possible to subvert the randomization process to ensure that a patient would be “randomized” to a particular group?	Yes. “In each center, sequentially numbered boxes containing to whole treatment for each patient were delivered to the investigator by the pharmacist following the order of the randomization list." (p. 2022) This should be sufficient to maintain allocation concealment.
3.	Were patients analyzed in the groups to which they were randomized?	No. Seven patients were excluded from the study. Two of these were later determined to have a phlebolith rather than a ureteral stone, two were determined to have proximal stones, one had a non-radiopaque stone. This was not, therefore, a true intention to treat analysis.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Uncertain. Although patients in the placebo group were more likely to be male, patients were similar with respect to age, weight, initial temperature and heart rate, and stone size. The authors do not provide additional demographic information, including medical comorbidities, history of prior stone, initial pain score, or baseline lab values (though they report no difference in serum creatinine or hepatic enzymes).
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	No. Patients randomized to the control group received matching placebo, produced by the same pharmaceutical company as the tamsulosin.
2.	Were clinicians aware of group allocation?	Yes. This was a "double-blind" study, and while not specifically mentioned, it seems reasonable to assume that clinicians were not made aware of group allocation.
3.	Were outcome assessors	Mostly yes. For the primary outcome, assessment was

	aware of group allocation?	made by the patients themselves, who were blinded. When confirmatory tests were performed (plain abdominal radiography or spiral tomodensitometry) it is not explicitly stated that radiologists interpreting these studies were blinded.
4.	Was follow-up complete?	Yes. Forty-days should be a sufficient duration of follow-up to ensure passage of the majority of stones.
II.	**What are the results ?**	
1.	How large was the treatment effect?	• The hazard ratio resulting from the comparison of time to stone expulsion distributions between randomization and day 42 was 1.27 (95% CI 0.81 to 2.04) in favor of tamsulosin. • Stone expulsion by 42 days occurred in 47 of 61 (77.0%) patients in the tamsulosin group and 43 of 61 (70.5%) patients in the placebo group (RR 1.1, 95% CI 0.88 to 1.4; p = 0.41). • There were 4 (6.6%) patients in the tamsulosin group and 6 (9.8%) in the placebo group requiring urgent hospitalization and ureteroscopy (RR 0.67, 95% CI 0.20 to 2.2; p = 0.51). • Pain relapse (which was not well-defined) occurred in 28 of 60 (46.7%) patients in the tamsulosin group and 35 of 59 (59.3%) patients in the placebo group (RR 0.79, 95% CI 0.56 to 1.1; p = 0.17). • No serious adverse events that could be attributed to placebo or tamsulosin were identified.
2.	How precise was the estimate of the treatment effect?	See above. This was a fairly small study, and 95% CI crossed one for all of the outcomes.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Likely yes. While the study was conducted in France, these were emergency department patients diagnosed with ureteral colic, although it is unclear how such diagnoses were made (CT. vs US vs. other). While these patients were admitted to the urology service for initial management, it seems unlikely that such admission would alter the outcomes.
2.	Were all clinically	No. The authors did not address overall quality of life or

	important outcomes considered?	cost of treatment. They did address the issue of pain by assessing pain relapses, but made no attempt to evaluate number of pain-free days or overall analgesic usage. While time to stone expulsion is frequently used in these studies, its value as a patient-centered outcome is limited if there is no pain associated with stone persistence.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. This small study found no benefit to tamsulosin usage in patients with distal stones between 2 and 7 mm in diameter. The majority of patients enrolled had stones that were 2-3 mm in size (> 70%), possibly eclipsing any benefit in patients with larger stones. Larger studies are necessary to evaluate for possible subgroups of stone size for which there may be benefit.

Limitations:

1. **The study was stopped after a sixth interim analysis recommended discontinuation, but the authors do not state how this decision was made (Problems of Stopping Trials Early). Additionally, there is no sample size analysis and the authors do not state what their planned sample size was.**

2. **The authors do not provide additional demographic information, including medical comorbidities or history of prior stone.**

3. **Stone size was 2-3 mm in over 70% of patients, which is fairly small in size (external validity). Some studies have suggested that tamsulosin is more effective in patients with larger stones (5-10 mm).**

4. **The primary outcome, time to stone expulsion, was based on patient-reported stone passage, which has been shown to be highly unreliable (Furyk 2016).**

Bottom Line:

This small, randomized controlled trial evaluating the use of tamsulosin in patients with distal ureteral stones between 2 and 7 mm in diameter found no benefit with regards to time to stone expulsion or need for urgent intervention. The vast majority of patients in the study had stones that were 2-3 mm in diameter, perhaps masking a possible benefit to patients with larger stones. Additionally, the trial was stopped early for unclear reasons, which may bias the results further.