Medical expulsive therapy in adults with ureteric colic: a multicentre, randomised, placebo-controlled trial

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Summary

Background Meta-analyses of previous randomised controlled trials concluded that the smooth muscle relaxant drugs tamsulosin and nifedipine assisted stone passage for people managed expectantly for ureteric colic, but emphasised the need for high-quality trials with wide inclusion criteria. We aimed to fulfil this need by testing effectiveness of these drugs in a standard clinical care setting.

Methods For this multicentre, randomised, placebo-controlled trial, we recruited adults (aged 18–65 years) undergoing expectant management for a single ureteric stone identified by CT at 24 UK hospitals. Participants were randomly assigned by a remote randomisation system to tamsulosin 400 µg, nifedipine 30 mg, or placebo taken daily for up to 4 weeks, using an algorithm with centre, stone size (≤5 mm or >5 mm), and stone location (upper, mid, or lower ureter) as minimisation covariates. Participants, clinicians, and trial personnel were masked to treatment assignment. The primary outcome was the proportion of participants who did not need further intervention for stone clearance within 4 weeks of randomisation, analysed in a modified intention-to-treat population defined as all eligible patients for whom we had primary outcome data. This trial is registered with the European Clinical Trials Database, EudraCT number 2010-019469-26, and as an International Standard Randomised Controlled Trial, number 69423238.

Findings Between Jan 11, 2011, and Dec 20, 2013, we randomly assigned 1167 participants, 1136 (97%) of whom were included in the primary analysis (17 were excluded because of ineligibility and 14 participants were lost to follow-up). 303 (80%) of 379 participants in the placebo group did not need further intervention by 4 weeks, compared with 307 (81%) of 378 in the tamsulosin group (adjusted risk difference 1·3% [95% CI –5·7 to 8·3]; p=0·73) and 304 (80%) of 379 in the nifedipine group (0·5% [–5·6 to 6·5]; p=0·88). No difference was noted between active treatment and placebo (p=0·78), or between tamsulosin and nifedipine (p=0·77). Serious adverse events were reported in three participants in the nifedipine group (one had right loin pain, diarrhoea, and vomiting; one had malaise, headache, and chest pain; and one had severe chest pain, difficulty breathing, and left arm pain) and in one participant in the placebo group (headache, dizziness, lightheadedness, and chronic abdominal pain).

Interpretation Tamsulosin 400 µg and nifedipine 30 mg are not effective at decreasing the need for further treatment to achieve stone clearance in 4 weeks for patients with expectantly managed ureteric colic.

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Introduction

Ureteric colic is defined as episodic severe abdominal pain from sustained contraction of ureteric smooth muscle as a kidney stone passes down the ureter into the bladder.[1] It is a common reason for people to seek emergency health care and was associated with 550 000 emergency room visits in the USA in 2009[2] (costing US$3 billion) and 25 000 hospital admissions in England in 2012[3] (costing £11·6 million). After clinical assessment and stone localisation by non-contrast CT of the kidneys, ureters, and bladder (CT KUB), patients can generally be managed at home with analgesia with the expectation of spontaneous stone passage.[1] The likelihood that the stone will pass within 4 weeks ranges between 50% and 95% depending on stone size and location in the ureter.[4] Expectantly managed patients who develop recurrent pain, sepsis, or compromised renal function need drainage if necessary followed by stone clearance using endoscopy or extracorporeal shock wave lithotripsy.[5]

Treatments that increase likelihood of stone passage would be expected to benefit patients with ureteric colic because the need for an interventional procedure will be reduced. The smooth muscle relaxant drugs tamsulosin (an α-adrenoceptor antagonist) and nifedipine (a calcium channel stabiliser) are possible agents, their use being termed medical expulsive therapy (MET).[6] Meta-analyses of data from randomised controlled trials (RCTs) report a statistically significant benefit for both tamsulosin and nifedipine over controls for the outcome of spontaneous stone passage[7,8] with tamsulosin better than nifedipine.[8] However, the clinical usefulness of MET is uncertain

Research in context

Evidence before this study

In planning our trial we identified two contemporary high-quality systematic reviews that had appraised and meta-analysed previous randomised controlled trials in this specialty. One was a Cochrane review that included trials of treatment with α blockers retrieved from the Cochrane Renal Group's Specialised Register up to July 9, 2012. Meta-analysis of 32 trials involving 5864 participants showed that use of α blockers increased likelihood of stone passage compared with control, with a relative risk (RR) of 1·48 (95% CI 1·33–1·64). Additionally, from four trials involving 3486 participants, tamsulosin seemed to be better than nifedipine at increasing the likelihood of stone passage (RR 1·19, 95% CI 1·05–1·35). Overall, the included studies were deemed to have a high or unclear risk of bias around masking and a low risk of bias around outcome collection and reporting. The second, a systematic review by Seitz and colleagues, searched Medline, Embase, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews up to Dec 31, 2008, for randomised trials of use of both α blockers and calcium channel stabilisers as medical expulsive therapy (MET). Combining all 29 studies involving 2419 participants, they noted that MET increased the likelihood of spontaneous stone passage (RR 1·45, 95% CI 1·34–1·57). Additionally, they found evidence from nine trials

involving 686 participants that nifedipine increased likelihood of stone passage compared with controls (RR 1·49, 95% CI 1·33–1·66). Overall, the trials were found to be of low-to-moderate quality on the basis of a validated scoring method.

Added value of this study

Both reviews emphasised uncertainty in estimates of effect due to the small size of most component studies, differences in inclusion criteria and outcome measurement, and inadequate masking of participants and assessors. We sought to overcome these deficiencies by designing a large, multicentre trial with robust means of concealment of allocated treatment. We also chose a clinically relevant, attributable, and clear primary outcome measure. Using this method we established that neither the most frequently used α blocker, tamsulosin, or the calcium channel stabiliser nifedipine showed any clinically useful benefit for increasing stone passage measured by the absence of need for further intervention.

Implications of all the evidence

Results of previous studies showed a positive benefit on spontaneous stone passage with these agents. However, our methodologically sound and large trial offers a strong evidence base for the alternative view that they are unlikely to be useful in the routine clinical care of people with ureteric colic.

because of the predominance of small, single-centre, low-to-moderate quality trials and variability in trial design with differing inclusion criteria and outcome measurement.[7,8] Despite these cautions and although not licensed for this indication, MET is recommended by clinical guidance[9] and is being adopted as part of routine expectant management.[10]

We now report the clinical results of the pragmatic randomised Spontaneous Urinary Stone Passage Enabled by Drugs (SUSPEND) trial, designed to resolve uncertainty about the benefit of these drugs when used in routine care of people with expectantly managed ureteric colic. We sought to establish whether tamsulosin or nifedipine increased the likelihood of spontaneous stone passage measured by the absence of need for further intervention and, if so, which was the better drug.

Methods

Study design and participants

In this randomised, placebo-controlled trial, we recruited patients presenting to 24 UK National Health Service hospitals with ureteric colic. Adults aged 18–65 years with one stone of 10 mm or less (at the largest dimension) in either ureter identified on CT KUB were included. Patients who were ineligible included those needing immediate intervention decided by clinical assessment, those with sepsis, those with an estimated glomerular filtration rate of less than

30 mL/min, and those already taking or unable to take an α blocker or calcium channel stabiliser. We excluded people older than 65 years because nifedipine dose titration is recommended for this age group. Full details of all inclusion and exclusion criteria are available in our published protocol.[11]

Patients gave written informed consent in line with Good Clinical Practice and the Declaration of Helsinki. The trial was approved by the East of Scotland Research Ethics Service (reference 10/S0501/31) and the UK Medicines and Healthcare products Regulatory Agency (MHRA; reference 2010-019469-26).

Randomisation and masking

Trained site personnel (research nurses and clinicians) enrolled participants at each site. Participants were allocated in a 1:1:1 ratio to either tamsulosin, nifedipine, or placebo by a remote randomisation system hosted at the Centre for Healthcare Randomised Trials (CHaRT) in Aberdeen, UK, using an algorithm with centre, stone size (≤5 mm or >5 mm), and stone location (upper, mid, or lower ureter) as minimisation covariates. Each randomly assigned participant was given 28 capsules of trial medication (over-encapsulated tamsulosin or nifedipine, or placebo) supplied by an independent source (Tayside Pharmaceuticals, Ninewells Hospital, Dundee, UK) who had no further involvement in the trial, ensuring that participants, clinicians, and trial personnel remained unaware of the allocated group.

Procedures

Participants self-administered tamsulosin 400 μg, nifedipine 30 mg, or placebo orally once daily until spontaneous stone passage occurred, the need for intervention was agreed, or until 4 weeks had passed since randomisation, whichever came first. We did not verify adherence to trial medication.

Baseline data were collected before randomisation in hospital. Local research staff obtained follow-up data by use of participant questionnaires, which were completed at home at 4 and 12 weeks, and case report forms, completed during clinic visits or telephone contact at 4 and 12 weeks. No clinical tests were mandatory as part of the trial protocol.

Safety outcomes were reported as and when they happened (via the case report form, patient questionnaires, and patient and clinician report). Suspected serious adverse events were graded at site by the local principal investigator, reported to the trial office to be confirmed by the chief investigator. Safety events were monitored by the sponsor, research ethics committee, and MHRA. Non-serious adverse events were not collected or reported.

Outcomes

The primary outcome was spontaneous stone passage in 4 weeks, defined as the absence of need for additional interventions to assist stone passage at 4 weeks after randomisation. Other outcomes were pain assessed by participant-reported number of days of analgesic use and visual analogue scale at 4 weeks, time to stone passage assessed by the date of imaging showing no stone at up to 4 weeks, health status assessed by the Short Form (SF)-36 questionnaire, and safety assessed by participant report of discontinuation of medication due to adverse effects and by serious adverse events monitoring. We also assessed health outcomes with the EQ-5D questionnaire, and heath-care resource use and participant costs (health economic components), the results of which will be reported elsewhere.

Statistical analysis

The trial was powered for the most conservative hypothesis: that the proportion of participants who passed their stone would be 10% higher in the tamsulosin group compared with the nifedipine group (85% vs 75%). We prespecified two comparisons, MET (tamsulosin or nifedipine) against placebo, and tamsulosin against nifedipine. We also made post-hoc comparisons of each agent against placebo. For 90% power and a type I error rate of 5%, we required 1062 participants (354 in each group), which we inflated to 1200 to allow for 10% loss to follow-up.

We use summary statistics to describe the characteristics of the trial groups at baseline and during follow-up. We used generalised linear models to analyse outcomes with adjustment for minimisation covariates,
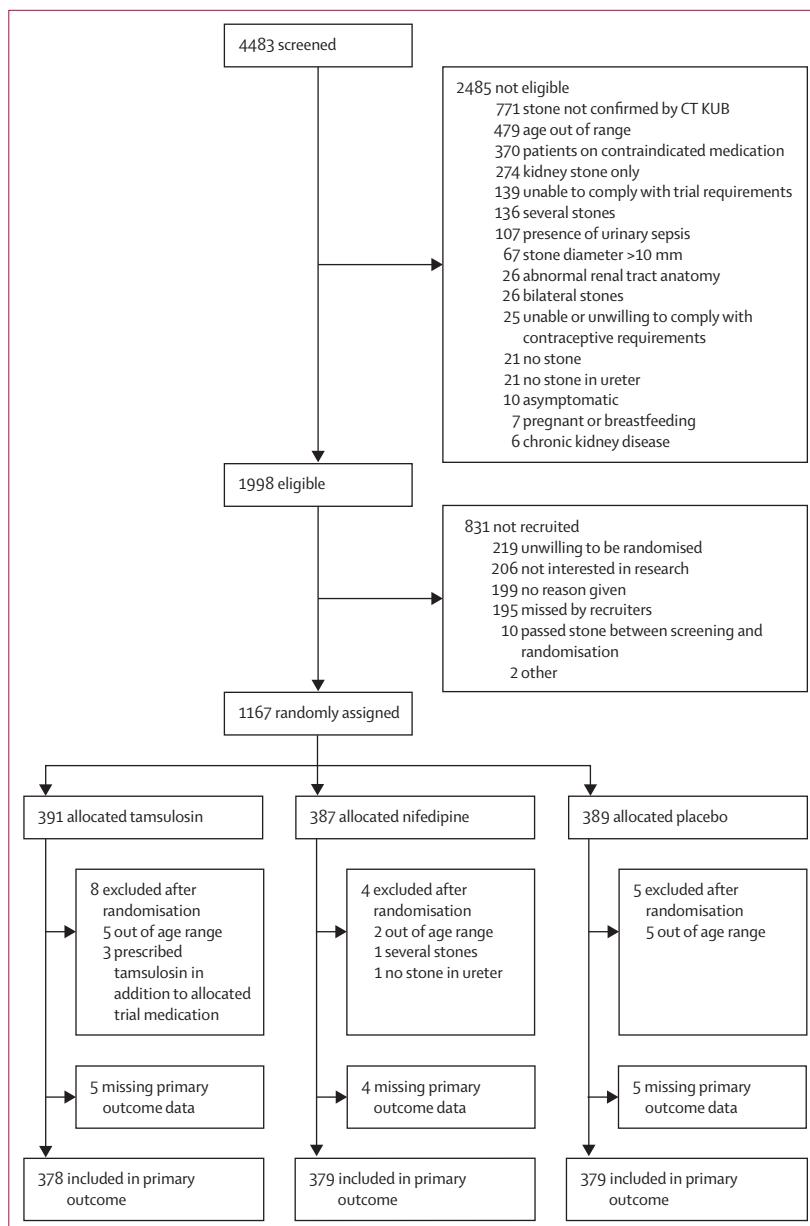

Figure 1: Trial profile
Numbers of participants declining further follow-up or not responding are cumulative in direction of participant flow. CT KUB=CT of the kidneys, ureters, and bladder.

logistic regression for binary outcomes, and linear regression for continuous outcomes. We present treatment effects with 95% CI; for the primary outcome we present both the odds ratio and absolute risk difference. We estimated CIs for the risk difference using the delta method. We analysed data for the primary outcome from the modified intention-to-treat population, which included all randomly assigned participants apart from those with missing primary outcome data and those who were found to be ineligible after randomisation. For secondary outcomes, we

	Tamsulosin (n=383)	Nifedipine (n=383)	Placebo (n=384)
Age, years	43·1 (11·5)	42·3 (11·0)	42·8 (12·3)
Women	68 (18%)	66 (17%)	85 (22%)
Stone size, mm	4·6 (1·6)	4·5 (1·6)	4·5 (1·7)
≤5 mm	287 (75%)	286 (75%)	286 (74%)
>5 mm	96 (25%)	97 (25%)	98 (26%)
Stone location			
Upper ureter	94 (25%)	89 (23%)	93 (24%)
Middle ureter	40 (10%)	43 (11%)	44 (11%)
Lower ureter	249 (65%)	251 (66%)	247 (64%)
History of previous stone episode	130 (34%)	118 (31%)	137 (36%)
Duration of pain, days	3·0 (5·1)	2·6 (3·3)	3·2 (5·5)
Pain visual analogue score*	4·0 (3·4)	3·9 (3·4)	3·6 (3·2)
Analgesic medication before admission			
Non-steroidal anti-inflammatory drug	132 (34%)	110 (29%)	117 (30%)
Opiate	63 (16%)	67 (17%)	81 (21%)
Other	79 (21%)	86 (22%)	79 (21%)
Analgesic medication on admission			
Non-steroidal anti-inflammatory drug	279 (73%)	289 (75%)	278 (72%)
Opiate	224 (58%)	230 (60%)	230 (60%)
Other	127 (33%)	141 (37%)	133 (35%)
Antibiotic medication on admission	38 (10%)	46 (12%)	41 (11%)
SF-36 physical score†	47·0 (9·0)	46·5 (9·2)	46·1 (9·7)
SF-36 mental score†	50·2 (10·8)	50·6 (10·8)	49·6 (11·6)

Data are mean (SD) and number (%). Data do not include participants who were excluded after randomisation. *Ranging from 0 (no pain) to 10 (worst imaginable pain). †Ranging from 0 (maximum disability) to 100 (no disability).

Table 1: Baseline characteristics in eligible, randomly assigned patients

	Odds ratio (95% CI); p value	Risk difference (95% CI)
MET vs placebo		
Unadjusted	1·04 (0·77–1·43); 0·76	0·8% (–4·1 to 5·7)
Adjusted	1·06 (0·70–1·60); 0·78	0·9% (–5·1 to 6·8)
Tamsulosin vs nifedipine		
Unadjusted	1·07 (0·74–1·53); 0·73	1·0% (–4·6 to 6·6)
Adjusted	1·06 (0·73–1·53); 0·77	0·8% (–4·5 to 6·1)
Tamsulosin vs placebo		
Unadjusted	1·08 (0·76–1·56); 0·76	1·2% (–4·4 to 6·9)
Adjusted	1·09 (0·67–1·78); 0·73	1·3% (–5·7 to 8·3)
Nifedipine vs placebo		
Unadjusted	1·02 (0·71–1·45); 0·93	0·2% (–5·4 to 5·9)
Adjusted	1·03 (0·68–1·56); 0·88	0·5% (–5·6 to 6·5)

MET=medical expulsive therapy.

Table 2: Primary outcome results, unadjusted and adjusted for stone location (lower vs middle vs upper ureter), stone size (≤5 mm vs >5 mm), and centre (random effect)

included participants in a complete case analysis under a missing-at-random assumption.

Sensitivity analyses assessed the effect of missing data on pain and health status outcomes.[12] First, we

repeated analyses using multiple imputation models with predictions based on all baseline covariates collected with results combined across ten imputed datasets. We then tested the robustness of these results using pattern mixture models, which imputed missing SF-36 scores across a range of potential values from minus half the observed SD to plus half the SD of the outcome being analysed.

All participants were analysed as randomised. Subgroup analyses explored the possible effect modification of stone size, location in ureter, and sex, all using treatment by subgroup interaction terms and 99% CI. Further details are available from our published protocol.[11] We did all analyses in Stata 13. An accompanying cost-effectiveness analysis will be reported separately.

Role of funding source

The funder (through their peer and funding board review process) approved the study proposal but had no role in the collection, analysis, or interpretation of data, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 11, 2011, and Dec 20, 2013, 1167 participants were randomly assigned (391 to tamsulosin, 387 to nifedipine, and 389 to placebo; figure 1). Of these, 17 were subsequently excluded because of ineligibility and 14 participants were lost to follow-up, and were not included in the primary outcome analysis. We were able to ascertain the primary outcome for 1136 (97%) participants in the final analysis. 719 (62%) of 1150 eligible participants completed the 4-week questionnaire and 564 (49%) of 1150 eligible participants completed the 12-week questionnaire, with no differences in the proportion returned between groups (data not shown). Baseline characteristics were similar for the three groups (table 1).

Spontaneous stone passage, defined by absence of need for intervention to assist stone passage during the 4 weeks after randomisation, did not differ between groups (table 2). 307 (81%) of 378 participants in the tamsulosin group needed no further intervention compared with 304 (80%) of 379 in the nifedipine group, and 303 (80%) of 379 in the placebo group. These findings were consistent across the predefined subgroups of sex, stone size, and stone location (figure 2). We also noted no difference in stone passage at up to 12 weeks (data not shown), by which time an additional 27 (7%) participants in the tamsulosin group, 25 (6%) in the nifedipine group, and 28 (7%) in the placebo group had an intervention planned. No differences were recorded in the secondary outcomes of days of analgesic use (table 3), time to stone passage (table 3), and health status between the groups (figure 3).
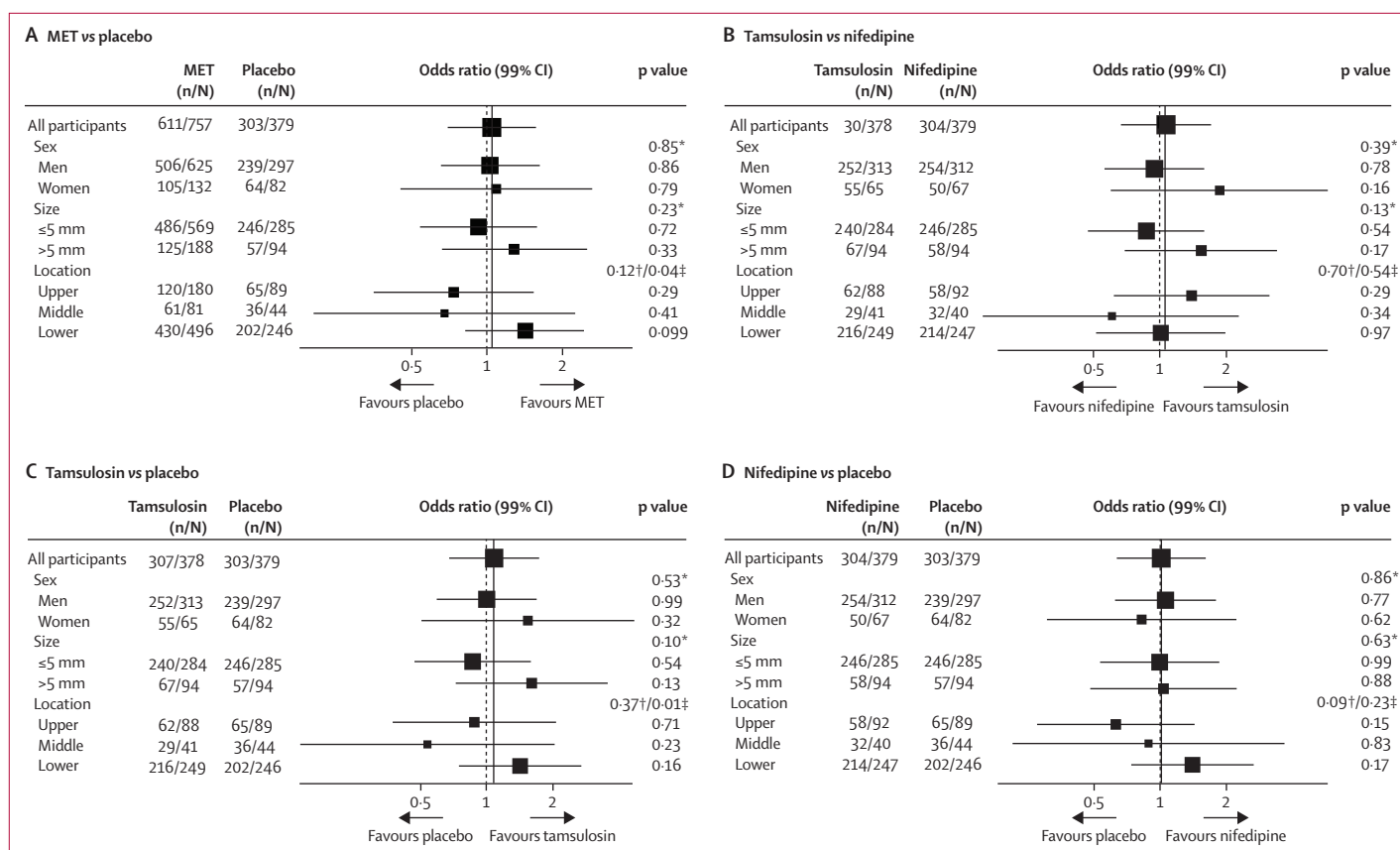
A MET vs placebo

	MET (n/N)	Placebo (n/N)	Odds ratio (99% CI)	p value
All participants	611/757	303/379		0.85*
Sex				
Men	506/625	239/297		0.86
Women	105/132	64/82		0.79
Size				0.23*
≤5 mm	486/569	246/285		0.72
>5 mm	125/188	57/94		0.33
Location				0.12†/0.04‡
Upper	120/180	65/89		0.29
Middle	61/81	36/44		0.41
Lower	430/496	202/246		0.099

Favours placebo — Favours MET (0.5, 1, 2)

B Tamsulosin vs nifedipine

	Tamsulosin (n/N)	Nifedipine (n/N)	Odds ratio (99% CI)	p value
All participants	307/378	304/379		0.39*
Sex				
Men	252/313	254/312		0.78
Women	55/65	50/67		0.16
Size				0.13*
≤5 mm	240/284	246/285		0.54
>5 mm	67/94	58/94		0.17
Location				0.70†/0.54‡
Upper	62/88	58/92		0.29
Middle	29/41	32/40		0.34
Lower	216/249	214/247		0.97

Favours nifedipine — Favours tamsulosin (0.5, 1, 2)

C Tamsulosin vs placebo

	Tamsulosin (n/N)	Placebo (n/N)	Odds ratio (99% CI)	p value
All participants	307/378	303/379		0.53*
Sex				
Men	252/313	239/297		0.99
Women	55/65	64/82		0.32
Size				0.10*
≤5 mm	240/284	246/285		0.54
>5 mm	67/94	57/94		0.13
Location				0.37†/0.01‡
Upper	62/88	65/89		0.71
Middle	29/41	36/44		0.23
Lower	216/249	202/246		0.16

Favours placebo — Favours tamsulosin (0.5, 1, 2)

D Nifedipine vs placebo

	Nifedipine (n/N)	Placebo (n/N)	Odds ratio (99% CI)	p value
All participants	304/379	303/379		0.86*
Sex				
Men	254/312	239/297		0.77
Women	50/67	64/82		0.62
Size				0.63*
≤5 mm	246/285	246/285		0.99
>5 mm	58/94	57/94		0.88
Location				0.09†/0.23‡
Upper	58/92	65/89		0.15
Middle	32/40	36/44		0.83
Lower	214/247	202/246		0.17

Favours placebo — Favours nifedipine (0.5, 1, 2)

Figure 2: **Subgroup analyses of the primary outcome**
Interaction analyses showing odds ratio (OR) and 99% CI for the primary outcome for the subgroups of participant sex (women vs men), stone size (≤5 mm vs >5 mm), and stone location (upper vs middle vs lower ureter). The graphs show relation to OR of 1 (dashed line) and trial estimate of OR (solid line) for each of the comparisons of MET versus placebo, tamsulosin versus nifedipine, tamsulosin versus placebo, and nifedipine versus placebo. MET=medical expulsive therapy. *p_interaction value. †p_interaction value between upper ureter and lower ureter. ‡p_interaction value between middle ureter and lower ureter.

Sensitivity analyses showed that these estimates were robust to assumptions about missing data for all but implausible scenarios (data not shown).

Serious adverse events were reported in three participants allocated to nifedipine (one had right loin pain, diarrhoea, and vomiting; one had malaise, headache, and chest pain; and one had severe chest pain, difficulty breathing, and left arm pain) and in one participant in the placebo group (headache, dizziness, lightheadedness, and chronic abdominal pain). No deaths were reported.

Discussion

The results of our trial, done in a routine care setting with masking of treatment allocation, showed that use of tamsulosin and nifedipine did not affect the proportion of patients needing further intervention to clear their stone during 4 weeks. This finding, suggesting similar rates of spontaneous stone passage across the trial groups, was consistent when possible modifiers of the likelihood of spontaneous stone passage were taken into account, and was unchanged at 12 weeks after randomisation. We found no evidence that the drugs reduced pain, hastened time to stone passage, or improved health state. The precision of trial estimates of treatment effect is sufficient to rule out any clinically useful benefit of these drugs to assist stone passage in this patient group at the dose and duration examined.

We used a pragmatic trial design in a multicentre setting to ensure that the drugs were tested in a manner aligned with present clinical practice recommendations, allowing direct translation of the results into standard clinical care. As recommended by a Cochrane review,[7] the key entry criterion was identification of one ureteric stone by CT KUB, ensuring that only patients with a symptomatic ureteric stone were included. The trial cohort was representative of the target population for MET with baseline characteristics such as stone size and location consistent with recent case series.[13,14] We chose to include treatment with tamsulosin as the α-adrenoceptor antagonist most often used for MET, and nifedipine since, at the time of trial design, both agents had been put forward as having efficacy at the dose and duration used in our trial to increase rates of spontaneous stone passage.[7,8] Inclusion of a placebo group, independent

	Tamsulosin	Nifedipine	Placebo	Difference (95% CI); p value
Pain variables				
Number of patients	247	239	231	
Any self-reported use of pain medication in first 4 weeks*	139 (56%)	133 (56%)	136 (59%)	
Number of days pain medication				
Mean (SD)	11·6 (8·7)	10·7 (9·0)	10·5 (8·2)	
Median (IQR)	10 (4–17)	7 (4–14)	7 (4–14)	
MET vs placebo†	..	..	..	0·6 (–1·6 to 2·8); 0·45
Tamsulosin vs nifedipine†	..	..	..	0·8 (–1·6 to 3·2); 0·50
VAS pain scale at 4 weeks				
Number of patients	233	231	216	
Mean score (SD)	1·0 (2·0)	1·3 (2·2)	1·2 (2·2)	
MET vs placebo†	..	..	..	0 (–0·4 to 0·4); 0·96
Tamsulosin vs nifedipine†	..	..	..	–0·3 (–0·7 to 0·1); 0·095
Time to stone passage				
Number of patients	79	74	84	
Mean time, days (SD)	16·5 (12·6)	16·2 (14·5)	15·9 (11·3)	
Median time, days (IQR)	14 (5–27)	13 (4–26)	14 (5–25)	
MET vs placebo				
Unadjusted	..	..	..	0·5 (–2·9 to 3·9); 0·78
Adjusted	..	..	..	0·6 (–2·6 to 4·0); 0·71
Tamsulosin vs nifedipine				
Unadjusted	..	..	..	0·4 (–3·7 to 4·4); 0·86
Adjusted	..	..	..	0·6 (–2·5 to 3·7); 0·72

All estimates adjusted for stone location (lower *vs* middle *vs* upper ureter), stone size (≤5 mm *vs* >5 mm), and centre (random effect). MET=medical expulsive therapy. VAS=visual analogue scale. *Percentages are derived from the number of responses available for each variable. †Adjusted.

Table 3: **Pain variables and time to stone passage**
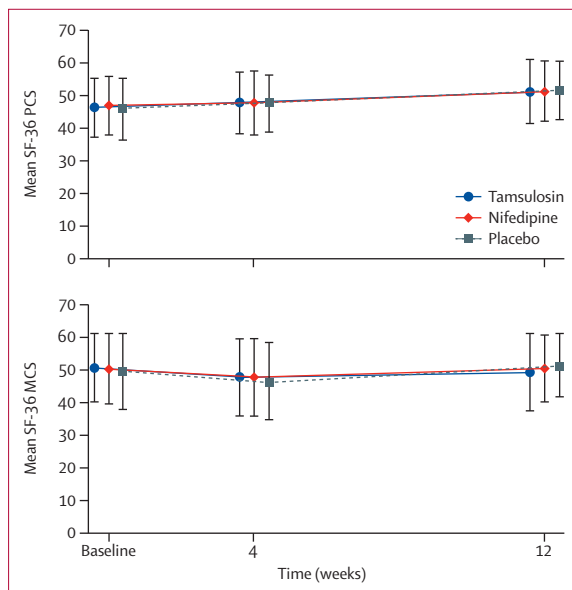
Figure 3: **Analysis of health status**
SF-36 mental component scores (MCS) and SF-36 physical component scores (PCS) for tamsulosin, nifedipine, and placebo groups at baseline, 4 weeks, and 12 weeks. Error bars show SD.

control of randomisation sequence, and over-en-capsulated trial medication supply ensured masking of participants, clinicians, and outcome assessors to allocation. We were able to collect data for the primary outcome for 97% of the large trial cohort, which surpassed the prespecified sample size. The design and completion to target of this trial therefore allows strong and clinically useful conclusions to be drawn concerning the lack of effectiveness of MET.

Our trial design differed from other trials in two ways that seekers of evidence regarding the use of MET will have to consider. First, we chose to have wide eligibility criteria, including patients with symptomatic stones of 10 mm or smaller (at the largest dimension) located at any site in the ureter. We chose these criteria because we could find no evidence to suggest that use of MET is more effective if targeted at specific patient groups categorised by stone size or site. Our choice is supported by present guidance that recommends MET but does not suggest any preliminary patient categorisation,[9,15] and although data are limited, this recommendation seems to have led to increasing use of MET.[10,16,17] Second, we focused on the absence of need for further intervention as the measure of spontaneous stone passage. We chose this endpoint as our primary outcome because it was consistent with the pragmatic study design assessing clinical effectiveness of the drugs. Having to undergo an intervention is a key outcome of interest for patients, signifying unresolved ill health with resultant costs. For clinicians it signifies the need to upscale care, and for health-care providers it drives requirement for additional capacity and funding. Other trials designed to have a low risk of bias have placed an additional lower limit on stone size, typically 3–5 mm, with or without a further restriction to patients with stones in the lower (distal) ureter at diagnosis.[8,18] The investigators of these trials reasoned that this patient group, with an expected proportion of patients with spontaneous passage of about 70%, were most likely to benefit from MET.[4] In planning our trial and considering the evidence, we believed that such subcategorisation was unwarranted and furthermore was unlikely to be feasible in routine emergency practice since it requires accurate stone measurement. Our study results, including the absence of any interaction between stone size or location and the primary outcome, gives us no cause to change this belief, although the trial was not formally powered for such subgroup analysis. We considered having imaging evidence of stone passage as a trial outcome, in common with other studies, but rejected it for two main reasons. Modalities with minimal radiation risk such as ultrasound and plain abdominal radiograph have inadequate diagnostic accuracy for the presence or absence of a stone,[19] whereas the definitive modality, CT KUB, has a radiation dose and cost that is sufficient to result in it not being recommended for this purpose by present clinical

guidance.[19,20] In our trial population, as in routine clinical care, further imaging was used when clinically indicated by continued pain, development of infection, renal dysfunction, or radiographic evidence of obstruction on diagnosis.[1] These findings were the clinical criteria against which the need for trial participants to undergo further intervention was judged.

The main reason for ineligibility noted during screening was use of an imaging method other than CT KUB for stone identification. The proportion of exclusions accounted for by this criterion fell from 43% to 25% during the recruitment period, suggesting an increase in compliance with diagnostic imaging guidance.[19] Scrutiny of baseline characteristics gives no suggestion that requirement for CT KUB diagnosis resulted in systematic differences between trial groups, although overall a greater proportion of women were excluded by this criterion than were men, possibly because of radiation concerns. The site initiation and monitoring protocol used in our trial gives confidence that the need for further intervention was accurately recorded by site staff masked to allocation. However, some participants might have had persistent asymptomatic stones that did not trigger further intervention by 4 weeks. Such participants would be expected to develop symptoms by 12 weeks and at this timepoint a further 80 participants in our trial had intervention planned, but a secondary analysis including these events did not change our finding of no difference between trial groups. The proportions of patients not needing intervention recorded in our trial populations—80% at 4 weeks and 73% at 12 weeks—is consistent with proportions reported in other cohorts.[4,21] The precision of our findings related to the large sample size gives confidence that the finding of no benefit for MET was not affected by the overall high proportion with spontaneous stone passage.

Collection of measurements in our trial for participant-reported secondary outcomes of pain control, time to stone passage, health status, and early discontinuation of trial medication, was incomplete. We found no evidence that the proportion of patients who completed measurements differed between treatment groups, although younger people were less likely to return questionnaires than older people (data not shown), in common with previous community-based trials.[22] Low response rates increase uncertainty around the finding of no effect for these secondary outcomes because of possible bias from missing data, but sensitivity analyses using imputation did not change the results. The amount of pain suffered and associated disturbance to social and working life are important characteristics of the disorder, but from an effectiveness trial design perspective are difficult to measure outside hospital in a sufficiently large sample for accurate estimation of any treatment effect. We also chose not to monitor adherence to trial medication to maintain simplicity and low participant burden. Despite these uncertainties we

noted no differences between study groups and particularly no evidence of any differential use of analgesics that might act as ureteric relaxants.

The aim of this trial was to provide a precise, unbiased estimate of benefit for MET in reducing need for further intervention to assist stone passage. We minimised allocation bias using a robust randomisation process and ascertainment bias by maintaining masking of all participants involved in the trial until data analysis, and recruited to a large target sample size with complete attribution of the primary outcome. These characteristics mean that results from our trial provide the highest quality evidence about clinical effectiveness of MET, since systematic reviews underpinning clinical guidance recommendations have all commented on the generally unclear risk of bias and low methodological quality of previous trials.[7,8,23] Differences in inclusion criteria, trial design, and outcome measurement limit the opportunity for qualitative or meta-analytical comparison of component trials reported in these reviews with our trial results. Concurrent with our trial, an alternative α-adrenoceptor antagonist, silodosin, has been studied with initial small trials suggesting benefit.[24,25] A subsequent multicentre trial reported that silodosin did not increase stone passage compared with placebo, although the prestated sample size was not attained, limiting certainty of the result.[18] Seekers of evidence often have to decide whether to base treatment decisions on a meta-analysis of several small low-quality trials typically showing larger differences, or on one large high-quality trial with a smaller effect size or a finding of no effect.[26] A recent review of this dilemma advises that judgments should involve careful consideration of qualitative and quantitative properties in each specific circumstance with further sensitivity analyses when possible.[27] Our judgment is that the results of our trial provide conclusive evidence that the effect of both tamsulosin and nifedipine in increasing the likelihood of stone passage as measured by the need for intervention is close to zero. Our trial results suggest that these drugs, with a 30-day cost of about US$20 (£13; €18), should not be offered to patients with ureteric colic managed expectantly, giving providers of health care an opportunity to reallocate resources elsewhere. The precision of our result, ruling out any clinically meaningful benefit, suggests that further trials involving these agents for increasing spontaneous stone passage rates will be futile. Additionally, subgroup analyses did not suggest any patient or stone characteristics predictive of benefit from MET.

Ureteric colic is a common, painful disorder and simple treatments that would make spontaneous stone passage more likely and quicker are still needed. Although α-adrenoceptor antagonists (tamsulosin) and calcium channel stabilisers (nifedipine) are ineffective, alternative classes of agents should continue to be identified and trialled.[28]

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