Use of drug therapy in the management of symptomatic ureteric stones in hospitalised adults: a multicentre, placebo-controlled, randomised controlled trial and cost-effectiveness analysis of a calcium channel blocker (nifedipine) and an alpha-blocker (tamsulosin) (the SUSPEND trial)

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Declared competing interests of authors: Professor John Norrie is a member of the National Institute for Health Research Health Technology Assessment Commissioning Board and a member of the National Institute for Health Research Efficacy and Mechanism Evaluation and Health Technology Assessment Editorial Boards.

Published August 2015
DOI: 10.3310/hta19630

Scientific summary

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Health Technology Assessment 2015; Vol. 19: No. 63
DOI: 10.3310/hta19630

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Ureteric colic describes the severe episodic pain people feel when a kidney stone passes down the ureter, which is the muscular tube connecting the kidney to the urinary bladder. It is a common reason for people to seek emergency help from the NHS in the UK, with 31,000 hospital admissions in England from April 2012 to March 2013. Ureteric colic predominantly affects people of working age, disrupting their social and economic activity. The stone will usually pass spontaneously within 4 weeks and patients are generally treated expectantly at home with general advice and painkillers. However, for about 25% of sufferers, failure of stone passage, the development of an infection or kidney damage means that active intervention to drain the affected kidney or remove the stone is required. This is more likely for those with larger stones or with stones higher up in the ureter. Recently, two drugs that relax the ureteric muscle have been identified and a series of small clinical trials suggest that their use during expectant management of people with ureteric colic reduces the likelihood of needing further intervention and hastens stone passage. Combining the results of these small trials in a meta-analysis suggests that people taking either of these drugs are about 50% more likely to pass their stone within 4 weeks compared with control and, when comparing the two drugs, the stone passage rate with tamsulosin hydrochloride (Petyme, TEVA UK Ltd) was about 10% better than with nifedipine (Coracten®, UCB Pharma Ltd). However, the trials were generally single centre and there was considerable clinical and statistical heterogeneity, which limits the applicability of the findings for the evidence base used as the basis for treatment decisions within the UK NHS. As a result, the National Institute for Health Research Health Technology Assessment programme commissioned a trial to determine precisely the effectiveness of these agents as medical expulsive therapy (MET) for people with ureteric colic and hence guide decisions around their use within the UK NHS.

Objectives

The research was designed to determine whether or not the use of MET is worthwhile for the UK NHS in terms of increasing the likelihood of spontaneous stone passage and being cost-effective compared with standard care without MET. The hypothesis for the SUSPEND (Spontaneous Urinary Stone Passage ENabled by Drugs) trial was that MET (tamsulosin or nifedipine) taken for up to 4 weeks would increase the proportion of spontaneous stone passage (measured as the lack of need for further intervention) by at least 25% compared with placebo control, and that tamsulosin would be at least 10% more effective than nifedipine.

We planned two comparisons of equal importance:

- MET (tamsulosin 400 µg or nifedipine 30 mg daily) versus placebo
- tamsulosin 400 µg daily versus nifedipine 30 mg daily.

Methods

Adults with ureteric colic presenting for urgent care, but not requiring immediate active treatment (i.e. without severe infection, uncontrolled pain or impaired kidney function), were identified from 24 UK NHS hospitals. Eligible participants had to have a single stone of a maximum dimension of $\leq$ 10 mm located within the ureter by computerised tomography of kidneys, ureters and bladder (CT KUB); to be able to take the trial drugs; and, for female participants, to agree to avoid pregnancy by using effective contraception during the 4-week trial period. After providing informed consent, eligible participants were randomised in a 1 : 1 : 1 ratio between the three groups using a remote telephone interactive voice response randomisation application that concealed allocation.

Relevant baseline data were collected by trial staff on a case report form (CRF) and from the participants by self-completed questionnaire. Participants were instructed to take the allocated medication once daily for up to 4 weeks, with early discontinuation if the stone passed, if further intervention was planned or if intolerable adverse effects occurred. The medications were supplied from an independent source using identical packaging and overencapsulation to maintain blinding of participants, clinicians and research staff. Outcome data and progress through the trial were recorded by participant questionnaires and CRFs at 4 weeks and 12 weeks after randomisation.

The primary outcome, spontaneous stone passage, was defined as the lack of need for further intervention to facilitate stone passage at 4 weeks. This was recorded on the 4-week patient questionnaire and 4- and 12-week CRFs. This was analysed using an intention-to-treat strategy by logistic regression. Treatment effects were summarised as odds ratios (ORs) and absolute percentage differences, both with 95% confidence intervals (CIs). Adjusted treatment effects were derived from models including fixed effects for stone size ($\leq$ 5 mm or > 5 mm) and stone location (lower, mid or upper ureter) at baseline, and a random effect for centre. The treatment-modifying effect of stone size and stone location was explored using tests of interaction. Secondary outcomes of health-related quality of life, pain and number of days of analgesic use at 4 weeks, and estimated time to stone passage were analysed using linear models. Within-trial cost-effectiveness over 12 weeks was examined by calculating costs in each group from NHS sources and quality-adjusted life-years (QALYs) based on participant completion of the European Quality of Life-5 Dimensions (EQ-5D™) questionnaire at baseline, 4 weeks and 12 weeks. The resultant cost–utility analysis was expressed as an incremental cost-effectiveness ratio and by cost-effectiveness acceptability curves.

Results

We randomised 1167 participants between January 2011 and December 2013, and included 1136 (97%) in our analysis of the primary outcome, thereby exceeding our planned sample size of 1080. There were 17 post-randomisation exclusions. Of these, 14 patients were randomised in error as they were found to be ineligible, whereas a further three were erroneously given open-label tamsulosin after randomisation before the trial medication was dispensed. The primary outcome data could not be determined for 14 participants. Baseline characteristics between the three trial groups were well balanced. Overall, the key characteristics of the SUSPEND trial population were similar to those seen in previous published cases series, except that we included a smaller proportion of women (19%). This was linked to a higher exclusion rate in women, predominantly as a result of lack of CT KUB. Participant-reported premature discontinuation of trial medication owing to intolerable side effects on the 4-week questionnaire was 6%, 10% and 17% in the placebo, tamsulosin and nifedipine groups, respectively. Trial medication contributed to three serious adverse events, but there were no deaths.

At 4 weeks, 303 out of 379 (80%) participants in the placebo group had passed their stone compared with 307 out of 378 (81%) allocated to tamsulosin and 304 out of 379 (80%) allocated to nifedipine. For the planned comparison of MET versus placebo the OR was 1.04 (95% CI 0.77 to 1.43) with an absolute difference of 0.8% (95% CI –4.1% to 5.7%), and for tamsulosin versus nifedipine the OR was 1.06 (95% CI 0.74 to 1.53) with an absolute difference of 1% (95% CI –4.6% to 6.6%). These estimates were unchanged in models adjusting for stone size and stone location. There was no evidence that the treatment effects differed across subgroups. There were no differences between the trial groups in terms of visual analogue pain score at 4 weeks, number of days of analgesic use or time to stone passage. Health status measured by the EQ-5D and Short Form questionnaire-36 items questionnaires improved in all groups between baseline and the 4- and 12-week time points to reach close to the norm for an age-matched UK general population. There were no differences at any time point between the trial groups. There was considerable non-response to participant questionnaires at 4 weeks and 12 weeks, but results were robust to sensitivity analyses exploring the effect of imputation of missing data using values maximally favouring active treatment. There were no differences in cost or gain in QALYs between the trial groups and, consequently, cost–utility analyses were uninformative. The lack of any differences meant that MET would not be considered to be cost-effective using the results from the trial.

Conclusions

The results of this large, multicentre, pragmatic, randomised controlled trial that focused on outcomes important to patients and the NHS show that MET using tamsulosin 400 µg or nifedipine 30 mg daily is not effective for increasing the likelihood of stone passage for people with ureteric colic over the 4 weeks after diagnosis. Estimated treatment effects and CIs rule out pre-specified clinically important differences. Relevant subgroup and sensitivity analyses did not identify any specific patient characteristics where benefit from MET was likely. There was also no evidence that use of MET reduced pain, hastened stone passage or increased quality of life compared with placebo. These results and a lack of any meaningful difference in costs mean that these drugs would be unlikely to be considered cost-effective for use in the UK NHS.

Implications for health care

Widely used clinical guidance documents, in line with the results of available meta-analyses, currently recommend the use of MET as part of the routine management of people with ureteric colic who would be expected to pass their stone spontaneously. Cohort studies suggest that the routine use of MET is increasing, with a recent estimate showing it was used in 60% of the target patient group. The finding of no effect from this large, high-quality trial (set within routine care for this condition) make it necessary for interested clinicians, clinical guideline writers and health-care policy-makers to reappraise the evidence to decide whether or not patients having expectant management for ureteric colic should be offered MET as part of their treatment. Contradiction of positive results derived from a meta-analysis of a series of earlier single-centre, small trials with varying risk of bias by the null results of an adequately powered high-quality trial with low risk of bias is a frequent phenomenon. Recent expert statistician opinion advises that seekers of evidence should make judgements after careful consideration of qualitative and quantitative properties in each specific circumstance, with further sensitivity analyses where possible. The SUSPEND trial clearly demonstrates the ineffectiveness of tamsulosin and nifedipine as MET at the therapeutic dose and duration used with a high degree of precision. Owing to the lack of congruence in trial design, it is not appropriate to combine our results in the previous meta-analyses. Instead, the results should be contrasted from both a quality and statistical perspective to shape clinical opinion and health-care policy.

Implications for research

The SUSPEND secondary outcomes reinforce the understanding that ureteric colic is a painful condition causing considerable disability and, hence, lowering the health state of sufferers. The pain and ill health largely resolve by 4 weeks, although a sizeable minority (20% in this trial) suffer continued problems related to the need for further active treatment to ensure eventual stone passage. The health-care need to lessen requirement for intervention, reduce pain and hasten stone passage therefore remains despite the demonstrated ineffectiveness of tamsulosin and nifedipine for MET. The main implications for research are as follows:

1. The precision of these results ruling out the > 10% effect size that might be considered to be the minimum clinically important difference makes further testing of these drugs futile.
2. A number of putative alternative agents targeted primarily at smooth muscle relaxation are being tested and, if initial assessment of efficacy is promising, should be explored further in a definitive multicentre trial rather than in small, single-institution studies.
3. Small, single-centre studies of novel treatments in urology carried out in different health systems may have limited generalisability as the basis for treatment decisions in the NHS. Clinicians, patients and health policy-makers should seek evidence from large, multicentre, UK-based trials, when available, before initiating change in clinical practice.

Trial registration

This trial is registered as ISRCTN69423238. This trial is also registered as European Clinical Trials Database (EudraCT) number 2010–019469–26.

Funding

Funding for this trial was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.116

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 08/71/01. The contractual start date was in June 2010. The draft report began editorial review in November 2014 and was accepted for publication in April 2015. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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