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Review

Alpha blockers should no longer be used for ureteric stones

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HIGHLIGHTS

- Alpha- blockers have been used in the treatment of ureteric stones, on the basis of small single-centered studies and meta-analyses of these.
- SUSPEND was a large placebo-controlled, double blinded study which failed to show any benefit from using alpha-blockers in these patients.
- Current evidence does not support the use of this off-label treatment in the management of patients with ureteric stones.

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ABSTRACT

Alpha-blockers have been used as medical expulsive therapy for ureteric stones for a number of years. Conventional wisdom supporting their use has recently been challenged by the publication of a large, multi-centre, randomised double-blinded, placebo-controlled study, SUSPEND, which showed that they were ineffective. This paper looks at the evidence behind the use of alpha-blockers, and discusses why we should believe the evidence we have from SUSPEND, rather than other published studies, and therefore stop using them as medical expulsive therapy.

1. Alpha-blockers for ureteric stones: where did we start?

The use of Alpha adrenoreceptor blockers has been an integral part of the conservative management of patients with ureteric stones for a number of years. Defined as “medical expulsive therapy” (MET), their use was adopted on the back of the publication of multiple studies showing a benefit of alpha-blockers, and meta-analyses of these studies showing similar outcomes [1,2].

In one of the first meta-analyses by Hollingsworth, data from 9 studies involving almost 700 patients showed that patients given alpha-blockers had a 54% greater likelihood of spontaneous stone passage compared to those not given the treatment. However, one of the main conclusions of the study was that, with respect to MET, “a high quality randomized trial is necessary to confirm its efficacy.” [1].

By the time Seitz et al. published their much reported meta-analysis 3 years later, the number of studies included had increased to 47, with a total of over 2400 patients. The pooled treatment effect of alpha-blockers and calcium channel antagonists, which have also been investigated as a MET agent, was 45%. Yet, despite this, based on a validated scoring method, the trials were found to be of low-to moderate quality with only 14 of 47 having a Jadad score of $\geq$3, with moderate heterogeneity and mild publication bias. Different alpha blockers were used, with different doses and different adjunctive medications. The study again made two important conclusions: “The vast majority of randomised studies incorporated into the present systematic review are small, single-centre studies, limiting the strength of our conclusions.”, and “multicentre, randomised, placebo-controlled trials are needed.”

A further analysis, the Cochrane Renal Group's meta-analysis [3] of 32 trials involving 5864 participants, showed that use of alpha-blockers increased likelihood of stone passage compared with control, with a relative risk (RR) of 1.48 (95% CI 1.33–1.64). Of the 32 studies, in only 7 were patients and doctors both blinded. In the other studies blinding was not described in the methods or no blinding had taken place. Two studies described incomplete data

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and one study showed a relatively high number of patients who withdrew from the study. It was felt that these factors limited the methodological strength of the evidence found.

Based on the available evidence at the time, in 2007, the EAU and AUA cooperative working group published a meta-analysis of MET [4]. The conclusions drawn were that alpha blockers increase rates of spontaneous stone passage and should be offered to patients.

2. How did we address concerns raised in early analyses of MET?

Responding to the deficiencies in the evidence highlighted by the above studies, McClinton et al. [5] designed SUSPEND (Spontaneous Urinary Stone Passage Enabled by Drugs), a large, double-blind multicentre trial with robust means of concealment of allocated treatment. They also chose a clinically relevant, attributable, and clear primary outcome measure, namely the requirement for further treatment within 4 weeks of randomisation. The study recruited 1167 adults with a single ureteric stone identified on CT, from 24 centres in the UK, who 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 ($\leq$5 mm or >5 mm), and stone location (upper, mid, or lower ureter) as minimisation covariates. The trial was registered with the European Clinical Trials Database, and as an International Standard Randomised Controlled Trial. Only 17 participants were excluded from the primary analysis. The results showed no benefit from active treatment. In the placebo group, 80% of patients did not need further intervention, compared to 81% in the tamsulosin group, with an adjusted risk difference of 1.3% ((95% CI −5.7 to 8.3); $p = 0.73$). There was a trend towards a benefit seen with MET (including nifedipine) for stones larger than 5 mm ($p = 0.33$), and for stones initially located in the lower ureter ($p = 0.099$), but neither of these was statistically significant.

3. Where has this left us?

Despite this high level evidence that had been lacking previously, which contradicted the findings of the previously published meta-analyses and reviews, a number of concerns were raised about the study. The main one was the choice of primary endpoint, namely need for intervention at 4 weeks, rather than confirmed passage of the stone radiographically [6]. A further concern was the low requirement for intervention at 80% in the control arm, compared to previous MET studies for which the radiographic spontaneous passage rate for rate for <10 mm stones in all locations in the ureter was 54% [2]. Due to these concerns about SUSPEND, a further meta-analysis conducted by the American Urological Association [6], but looking only at distal ureteric stones, did not even incorporate the SUSPEND data, for the reasons given above. Their analysis showed superior stone-free rates for those patients treated with a-blockers (77.3%) compared with placebo or no treatment (54.4%), incorporating a total of 27 studies, totaling 1215 patients, but with a mean number of patients per study of only 45. They concluded that “the recommendation for MET in properly selected patients still stands until further compelling studies suggest otherwise.”

It is worthwhile considering whether the concerns which have been raised about SUSPEND are valid. The first relates to the use of the requirement for intervention as a primary endpoint. This is a clinically relevant endpoint, is definitive and measurable. CT scans of all patients to confirm stone passage was not routine practice in the UK, and is not required in a number of cases. The need for intervention is a more reliable outcome than stone free rate, as reported by the patient or measured by different imaging modalities. Indeed, many of the studies used in the meta-analyses mentioned do not have CT confirmation of stone passage as an outcome measure, but use patient recollection, which is known to be unreliable. For example, from 22 studies included in the Cochrane review [3] that compared tamsulosin 400 μg with control, only 3 studies mandated the use of CTKUB for follow up [7].

Thus, we would agree that while the outcome measure chosen is not a traditional one, it is a relevant and more definitive one than that used in many studies included in meta-analyses, and the concerns about its use do not invalidate the findings of the study.

The second concern relates to the high rates of absence for the need for intervention reported in the SUSPEND study, at 80% in the control group. While high, such high rates of spontaneous stone passage have been reported previously. Indeed, in the Seitz meta-analysis of 2009 [2], 3 studies reported spontaneous passage of stones at 70% of greater, with one of these reporting stone free rates at 77% [8]. A more recent randomised, double-blind, placebo-controlled, multicenter trial of 403 patients with ureteric calculi which used CT confirmation of stone passage as the primary outcome measure, found spontaneous stone passage rates of 82% in the control group [9]. Interestingly, this study, despite the similarly high spontaneous passage rate to SUSPEND, has been included in the meta-analysis done by the AUA [6]. In fact, of the 32 studies included in this meta-analysis, 4 have been included where spontaneous stone passage rates are $\geq$70%, and in two of these the rates are $\geq$80%. Furthermore, this meta-analysis also includes two studies where the rates of spontaneous stone passage are $\leq$20%, which also represent an approximate 30% difference from the mean spontaneous passage rate of previously published studies. We would therefore also suggest that this concern regarding SUSPEND does not make the findings of the study less valid.

A further concern regarding the use of alpha-blockers is the side effect profile. Often dismissed a minimal, they are described as having a “low side effect profile” in the AUA guidelines [6]. There have been concerns however, about their hypotensive effects, especially at initiation of treatment, in the elderly, and in those on concomitant vasodilator drugs [10]. It should also be noted, and patients must be told, that it’s use as MET is “off-label”, and there is no safety data for its use in women.

4. What should we believe?

It is important that we are not misled by the evidence, and that there is a clear and robust method for choosing which evidence to primarily base our management decisions on, or indeed include in reviews or meta-analyses. We have already discussed the reasoning given for including some studies when collating evidence, but not others, which may not stand up to scrutiny. However, another question is whether we should believe a well performed multicentre study, or a meta-analysis of multiple small studies. On this question we know that small studies lead to publication bias, something which was acknowledged by Seitz [2], and small single-center RCTs tend to show larger treatment effects than multicenter RCTs usually do [11,12]. In looking at the 32 studies included in the AUA meta-analysis [6], only 9 included $\geq$100 patients, and the variation in stone passage rates across the studies included was from 4 to 82%. This is a huge variation, and likely results from heterogeneity of stone sizes included, as well as other factors such as variability in concomitant medications and timing of and method to determine stone free status. This variation is much less likely explained by biological variability.

It has also been suggested that well performed, large, multicenter, placebo-controlled RCTs should be assigned a higher level of evidence than meta-analyses of small RCTs, which themselves

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should be used help generate hypotheses for larger RCTs which would then help obtain reliable overall answers [13]. This is exactly what SUSPEND, one such large multi-centre, double-blinded, placebo-controlled, properly powered RCT of over 1100 patients, has done. We should believe it.

Ethical approval

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Author contribution

Oliver J Wiseman and Sam McClinton.

Both authors contributed to the manuscript, and reviewed the final version.

Conflicts of interest

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