Tamsulosin and nifedipine in ureteric colic managed expectantly


CLINICAL QUESTION: Are smooth muscle relaxant drugs like tamsulosin and nifedipine useful in assisting stone expulsions in patients managed expectantly for ureteric colic?

AUTHORS’ CONCLUSION: The results of the trial provide conclusive evidence that both tamsulosin and nifedipine are ineffective in increasing the likelihood of stone passage (as measured by the need for intervention within 4 weeks) in patients with ureteric colic managed expectantly. There is no clinically meaningful benefit even with a longer time period (12 weeks), and in subgroups of differing stone sizes and location.

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. Between 50-95% of ureteric stones are passed out in the urine spontaneously within 4 weeks (depending on stone size and location in the ureter) with expectant management. Those who develop recurrent pain, sepsis or compromised renal functions will need stone clearance using endoscopy or extracorporeal shock wave lithotripsy.

Smooth muscle relaxant drugs tamsulosin (and α – adrenoceptor antagonist) and nifedipine (a calcium channel blocker) are two drugs that have been used to assist in the expulsion of the stone in patients who are managed expectantly. This is termed Medical Expulsive Therapy (MET). There have been some studies and meta-analyses that have studied the usefulness of these drugs in expectant management but it is not clear whether these drugs actually offer any kind of clinical benefit.

To answer this question, the authors conducted a randomized, placebo-controlled trial involving 1167 adults in 24 hospitals in the UK, who were randomized to a tamsulosin group, nifedipine group and placebo group. The tamsulosin and nifedipine groups were compared with each other and with the placebo group, both together and separately. The primary outcome was spontaneous stone passage in 4 weeks, defined as the absence of need for additional interventions to assist in stone passage.

RESULTS

1. Spontaneous stone passage did not differ significantly between the groups (81% of tamsulosin, 80% of nifedipine group and 80% of placebo group had spontaneous stone passage.) [MET vs Placebo – OR-1.06, CI-0.7-1.6, p= 0.78; tamsulosin vs nifedipine – OR-1.06, CI-0.73-1.53, p=0.77].

2. These results were similar in the subgroups of sex, stone size and stone location. There was no difference even after 12 weeks in an analysis done separately.

3. Serious side effects were
seen in three participants in the nifedipine group and in one participant in the placebo group; there were no deaths.

DISCUSSION

This well-conducted study showed that in a routine care setting, there was no meaningful clinical benefit in administering smooth muscle relaxant drugs like tamsulosin and nifedipine in patients with ureteric colic who are being managed expectantly. This lack of benefit was consistently seen even when adjusted for possible confounders and in different subgroups of gender, stone size and locations.

For clinicians, this is important since it clarifies the question whether patients who are on expectant management need to be on medications. For both clinicians and patients, this also means decrease in costs and safety (in terms of possible adverse effects). The strength of the study was that it was prospective and randomised with both the patients and trial personnel being blinded to the type of medication prescribed. The number of participants was much larger than in previous studies. One drawback was that only tamsulosin and nifedipine were included in this study and this does not exclude other drugs like silodosin (an α-adrenoceptor antagonist) which has shown some benefit in smaller trials.

Expert Comments:
Dr. Anuj Deep Dangi, Assoc. Prof., Dr. Nitin S. Kekre, Professor, Dept. of Urology, CMC Vellore
This is well conducted clinical trial answering a clinically relevant question, keeping the cost of treatment to society in mind. A purist might point out the fact that end point of the study was not radiologically proven clearance of stone, rather lack of need for intervention, however it is not standard clinical practice to confirm the passage of stone by NCCT KUB for obvious reasons (radiation exposure and costs involved). The conclusion can be safely extrapolated to our daily clinical practice i.e. Tamsulosin (400 micrograms) and Nifedipine (30 mg) in daily dosage does not reduce the risk of surgical intervention for a ureteric calculus of size ≤ 10 mm and thus should be avoided.

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Serum phospholipase A2 as a biomarker for snake envenomation

Source: Diagnosis of snake envenomation using a simple phospholipase A2 assay. Maduwage K, O'Leary MA, Isbister GK. Scientific Reports. 2014 Apr 29;4:4827. Summary prepared by Dr. Anand R, Department of Biochemistry, CMC Vellore

Research question: Phospholipase A2 is a known component of snake venoms; can activity of the enzyme be used as a biomarker for snake envenomation.

Main finding: Serum phospholipase A2 activity is non-specifically elevated in cases of snake envenomation and can be a potential biomarker to diagnose systemic envenomation.

Background
Mortality and morbidity associated with snake bites are a major problem in tropical nations, especially the rural areas.1 There are no accurate laboratory tests that help in the diagnosis of systemic envenomation. A 20-min whole blood clotting test is commonly used for the diagnosis of coagulopathy in these patients.2 However, the unreliability of the test in diagnosis of early envenomation and in snake bites not associated with coagulopathy are major concerns.3-5 The enzyme phospholipase A2 (PLA2) is a common component of most snake venoms and is widely used to study activity of venoms, but whether assaying its activity would aid the diagnosis of snake envenomation is not known.
Methods
The authors estimated activity of PLA2 in pre-antivenom samples of 77 patients diagnosed with systemic snake envenomation based on data from clinical and coagulation studies. This group mainly comprised of envenomation due to Russell’s viper (Daboia russelii; N=32) and hump-nosed pit viper (Hypnale hypnale; N=35) envenomation; there were also 3 patients with Indian cobra (Naja naja) envenomation, 2 with Indian krait (Bungarus caeruleus) envenomation, 5 with red-bellied black snake (Pseudechis porphyriacus) envenomation. Comparison was made against 31 patients with history of snake bite but no evidence of systemic envenomation.

Results
It was seen that serum PLA2 activity was significantly higher in patients with snake envenomation; highest activity was noted specifically in Russell’s viper envenomation. The activity of PLA2 showed good correlation to the concentrations of venom in these patients. Interestingly, PLA2 activity showed good correlation to free venom concentrations. Following antivenom administration, there was a decrease in the activity of PLA2 while patients with venom recurrence had an increase in PLA2 activity after a brief fall.

Discussion
Considering that PLA2 activity was elevated non-specifically in most cases of envenomation irrespective of the cause, the test cannot help identify the species of the snake. However, PLA2 activity closely followed venom concentrations; higher activity of the enzyme was seen with large venom doses and this activity decreased following antivenom administration. Hence, PLA2 activity can help in assessing the degree of envenomation, effectiveness of antivenom treatment and thus shows potential as a good index of systemic envenomation. Since PLA2 activity is non-specifically elevated, it could also be useful in cases of snake bites not associated with coagulopathy, especially the neurotoxic species. Some limitations of the study are that the time that elapsed between snake bite and sampling is not known. The kinetics of PLA2 appearance in blood is also not studied, hence the earliest time point at which the test could be performed is not clear.

References

Expert comments: Dr. Victoria Job, Professor & head, Department of Clinical Biochemistry, CMC Vellore
PLA2 is a family of enzymes grouped as secretory PLA2 (PLA2s), Cytosolic PLA2 (PLA2c) and LP-PLA2 which has the Platelet activating factor and is an artherogenic marker. The secretory enzyme PLA2s is found in many mammalian tissues mainly pancreas and kidney and in insect and snake venom. The study clearly shows a good correlation of its serum levels with different types of snake envenomation and levels regressing with anti venom administration. It definitely could be used as a diagnostic test to confirm snake bites, to assess the extent of envenomation, to guide therapeutic decisions and also to monitor the victim. Spectrophotometric assays can be made available in mid level laboratories to aid in the management
of snake bite patients. It would be a good test to be made available in a tertiary care centers where many such patients are medically managed.

PLA2s is increased in many inflammatory conditions but has not come into regular use since other good markers which have established measurement techniques are available. Many studies have been conducted of its usefulness in pancreatic diseases. In acute pancreatitis high levels were seen, in chronic and pancreatic cancer abnormal levels were seen and with severe exocrine insufficiency the levels were very low. It did not seem to add any additional information than Serum Amylase and Lipase so is not used as a routine test of pancreatic function. PLA2s has been shown to be increased in cardiovascular diseases too but the Lipoprotein associated PLA2 has a better correlation.

UPCOMING EVENTS IN CMC VELLORE

11th Conference of Indian Society for Bone and Mineral Research (ISBMR)

- **Date:** 27th & 28th November 2015
- **Pre-conference CME on Metabolic Bone Disorders on 26th November 2015**
- **Venue:** Scudder Auditorium, CMC, Vellore.
- **Who can attend:** This is a conference for General Physicians, Endocrinologist, Nutritionists, Nephrologists, Paediatricians, Nuclear Physicians, Rheumatologist, Endocrine and Orthopaedic Surgeon.
- **For more details kindly visit the website:** [www.isbmr2015vellore.in](http://www.isbmr2015vellore.in)

WORKSHOP ON THERAPEUTIC DRUG MONITORING

organized by Clinical Pharmacology Unit, Department of Pharmacology & Clinical Pharmacology, Christian Medical College, Vellore

- **Date:** November 30th - December 3rd – 2015
- **Registration and Fees:** The cost of the workshop is Rs 4,500/- . This includes the workshop handouts, lunch and refreshments. Early registration up to 10th November 2015. Late registration up to 20th November 2015 Cost = above fees + Rs 500/-. Please make the Demand Draft in favour of “CMC Vellore Association” payable at Vellore and send it to the address given below.
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