

## A Prospective, Randomized, Controlled Study to Evaluate the Efficacy and Tolerability of Ayurvedic Formulation “Varuna and Banana Stem” in the Management of Urinary Stones

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### Abstract

**Background:** Medical management of urinary calculus disease is a challenge for modern science. In the present trial Ayurvedic drug “Herbmed,” which is made up of varuna (*Crataeva nurvala*) and banana stem (*Musa paradisiaca*) was assessed to see reduction and/or expulsion of urinary calculi and also to assess the role of these drugs to reduce pain during expulsion.

**Materials and methods:** In this prospective randomized, double-blind, placebo control trial, total 77 patients with calculi more than 5 mm were included. All patients were evaluated either by X-ray KUB or USG KUB for 3 months. All patients were divided into two groups: group A included patients with calculi 5–10 mm ( $n = 31$ ) and group B with calculi  $> 10$  mm ( $n = 30$ ) with either active treatment or placebo in both the groups. All patients were asked to keep a record of number of pain episodes, while severity of pain was measured on a visual analogue scale (VAS).

**Results:** In group A, there was 33.04% reduction in the size of calculi in the active arm while there was a 5.13% increase in the same group in the placebo arm ( $p = 0.017$ ). In the other group B, there was an 11.25% reduction in the active arm and a 1.41% reduction in the same group with placebo. In the active arm there was statistically significant lower VAS as compared to the placebo arm in the form of the highest VAS ( $p = 0.008$ ), average VAS ( $p = 0.001$ ) and VAS at the first episode of pain ( $p < 0.0001$ ).

**Conclusions:** Our preliminary experience suggests that the Ayurvedic formulation “varuna and banana stem” has promise for the management of upper urinary-tract calculi, especially renal calculi. It helps to dissolve renal calculi and facilitate their passage. In addition, it also helps in reduction of pain due to renal/ureteric calculus disease. A larger phase III study with a longer follow-up is required.

### Introduction

Urinary calculus disease is as old as humanity. Urinary calculi have been found in the tombs of Egyptian mummies dating as far back as 4000 BC.<sup>1</sup> Reference to stone formation is made in early Sanskrit documents found in India between 3000 and 2000 BC.<sup>2</sup> Calcium-containing calculi, especially calcium oxalate monohydrate (whewellite), calcium oxalate dihydrate (weddelite), and basic calcium phosphate (apatite), are the most common, occurring to the extent of 75–90%; followed by magnesium ammonium phosphate (struvite) at 10%–15%, uric acid at 3%–10%, and cystine at 0.5%–1%.<sup>3,4</sup> The possibility of renal calculus disease occurring over a lifetime is estimated at 1%–15%, with the calculi

likely to vary according to age, gender, race and geographic location.<sup>5</sup> Urinary calculus occurrence is relatively uncommon before the age of 20 but peaks in the fourth to sixth decades of life, and is more common in males than females.<sup>6</sup>

In the Indian traditional system of medicine, most remedies were made from plants though the rationale behind their use has not been well established through systematic pharmacologic and clinical studies. Our main area of interest was the role of herbal drugs in the treatment of upper urinary tract calculi, and we researched ancient Ayurvedic literature that emphasized the use of herbal medicines.<sup>7</sup> Many herbal preparations for treating calculus disease have been described, however proper scientific study has not been carried out on these medicines (PubMed, Cochrane Collab-

oration, MEDLINE,<sup>®</sup> etc., checked). There are many references to medical treatment of ureteric calculi, but very few systematic prospective randomized studies have been carried out for either expulsion and/or dissolution of the renal calculus. In the present trial, two plants have been selected, varuna and banana (Herbmed<sup>®</sup> is the name given to the mixture of varuna and banana stem). Herbmed is a brand name and it contains varuna (*Crataeva magna* [Lour.] DC. Synonym *Crataeva religiosa* var. *nurvala* [Buch.-Ham.] Hook f and Thomas) and banana (*Musa paradisiaca* Linn.) The application for the patent is pending.

The varuna bark, *Crataeva nurvala* (Linn name-*Crataeva magna* [Lour.] DC. Synonym *C. religiosa* var. *nurvala* [Buch.-Ham.] Hook. f and Thomas)<sup>8</sup> has been extensively studied by a number of investigators in India. The Pharmacology division of the Central Drug Research Institute in Lucknow, India, has carried out detailed pharmacological and chemical studies on this plant.<sup>9</sup> The active constituent of varuna is lupeol; a pentacyclic triterpene with antiurolithiatic activity.<sup>10–13</sup> The banana plant (*M. paradisiaca* Linn.)<sup>14</sup> is known to be a useful agent in urolithiasis.<sup>15</sup>

## Materials and Methods

As per GCP norms, we sought approval from the ethical committee of the Arogyaseva Medical Academy of India prior to the study. This prospective, randomized, placebo controlled, double-blind, phase 2 trial was conducted at the AMAI Trust Multispecialty Hospital, Pune, India, from July 2007 to February 2008. Only the manufacturer was aware of the content of the drug, with both the investigators and patients remaining blind. Calculi of 5-mm size or more were included while patients with acute conditions of renal/ureteric calculi, active localized or systemic infections including active urinary tract infection, or any systemic disease requiring other medication or surgery were excluded. Randomization was done by the envelope method. All patients were evaluated by X-ray KUB except those in whom the stone was either radiolucent or faintly seen, where USG KUB was used as a primary evaluation. The X-ray KUB was used to calculate the surface area of each stone based on length and width.<sup>16</sup> For calculi followed up by USG KUB, the largest diameter of a stone was considered instead of the surface area. The cumulative diameter was calculated for subjects with multiple calculi. All patients were prescribed one capsule in the morning after breakfast and one capsule in the evening after dinner (either Herbmed or placebo). Each capsule of Herbmed contains 250 mg *C. nurvala* and 250 mg *M. paradisiaca*. All patients were asked to maintain a record of the number of pain episodes, while severity of pain was measured on a visual analogue scale (VAS).<sup>17</sup> All patients were also prescribed diclofenac (50-mg tablet or 2-cc intramuscular injection) for unbearable pain and advised to keep a record. The primary endpoint of the study was on completion of a 3-month period, or complete expulsion of a stone.

A total 98 patients were screened, of which 77 were included and 61 had reached the primary endpoint. Decoding was done at the end of 3 months. All patients were divided into two groups. Group A included patients with stone size 5–10 mm ( $n = 31$ ) either on the active drug ( $n = 23$ ) or on the placebo ( $n = 8$ ); group B included patients with stone size more than 10 mm either on active drug ( $n = 24$ ) or

placebo ( $n = 6$ ). SPSS software was used to analyze the study data.

## Results

In the active arm of group A ( $n = 23$ ), complete expulsion ( $n = 5$ , 21.7%), reduction ( $n = 11$ , 47.82%), no change ( $n = 4$ , 17.39%), and increase in size ( $n = 3$ , 13%) of the stone were noted. In the placebo arm of group A ( $n = 8$ ), reduction ( $n = 3$ , 37.5%), no change ( $n = 2$ , 25%), increase in size ( $n = 3$ , 37.5%), and no complete expulsion was noted.

In the active arm of group A there was 33.04% reduction in either surface area or size while in the placebo arm there was 5.13% increase in the same ( $p = 0.017$  by unpaired  $t$ -test).

In the active arm of group B ( $n = 24$ ), reduction ( $n = 14$ , 58.34%), no change ( $n = 7$ , 29.16%), and increase of the stone size ( $n = 3$ , 12.5%) were noted. In the placebo arm of group B ( $n = 6$ ), reduction ( $n = 1$ , 16.67%), no change ( $n = 2$ , 33.34%), and increase ( $n = 3$ , 50%) was noted.

In the active arm of group B, there was an 11.25% reduction in either surface area or size of calculi, while, in the placebo arm, there was a 1.41% reduction in the same ( $p = 1.134$ , unpaired  $t$ -test). The power of the test was 91.8%. The VAS scores of both groups A and B were comparable. The highest VAS, average VAS and VAS at first episode of pain were also compared. In the active arm, the VAS was lower as compared to the placebo arm in the form of the highest VAS ( $p = 0.008$ , Mann-Whitney test), average VAS ( $p = 0.001$ , chi-square test), and VAS at first episode of pain ( $p < 0.0001$ , Mann-Whitney test). The need for diclofenac was significantly lower in the active arm as compared to the placebo arm ( $p < 0.0001$ ). No major adverse reaction in either arm was seen. Minor adverse reactions such as nausea, giddiness, and epigastric pain were seen in both active and placebo arms, and were comparable.

## Discussion

Mentioned in ancient literature, stone disease is even today one of the most common afflictions of society. With Westernization of global culture, however, the site of stone formation has migrated from the lower to the upper urinary tract.<sup>6</sup> There are many treatment options for upper urinary tract calculi, including open surgery, endoscopic procedures such as ureteroscopy, percutaneous nephrolithotomy (PNL), and extracorporeal shockwave lithotripsy (SWL), but they are not free from complications.<sup>18–20</sup> Burgher et al., in their 3.26-year follow up study of asymptomatic renal calculi, showed that 77% of a study population demonstrated progression, with 26% requiring intervention.<sup>21</sup> Prasad et al. have done a study on different herbal drugs in urolithiasis.<sup>22</sup> In this study, herbal treatment for urinary calculi, litholytics are used to “dissolve” the calculi or aid their passing to guard against further retention.

As mentioned earlier, Herbmed contains two active components; *C. nurvala* and *Musa paradisiaca*. The effect of oral administration of *C. nurvala* bark decoction on calcium oxalate lithiasis has been studied in rats. The elevation of the oxalate-synthesizing liver enzyme, glycolate oxidase, produced by feeding glycolic acid was remarkably reduced with the decoction, showing a regulatory action on endogenous oxalate synthesis. The increased urinary excretion of the crystalline constituents along with lowered magnesium excre-

tion found in stone-forming rats was partially reversed by decoction treatment.<sup>23</sup> Lupeol, a triterpene compound has been isolated from *C. nurvala* and was shown to have dose related prophylactic and curative activities in albino rats when studied by the foreign-body insertion method using glass beads.<sup>24</sup> Lupeol also showed a significant dose related antioxaluric and anticalciuric effect in rats against hydroxyproline-induced hyperoxaluria.<sup>11,12</sup> A number of lupeol derivatives have been synthesized and studied in rats for their antioxaluric and anticalciuric effects against hyperoxaluria.<sup>13</sup> Some of these derivatives exhibited better antioxaluric and anticalciuric activity when compared to the parent compound lupeol. The effect of *C. nurvala* bark decoction on calcium oxalate urolithiasis induced by 3% glycolic acid has been studied in rats.<sup>25</sup> The decoction showed significant activity in preventing the deposition of calcium and oxalate in the kidney by inhibiting the activity of the liver enzyme glycolic acid oxidase. Treatment with *C. nurvala* bark decoction was reported to lower the levels of intestinal Na<sup>+</sup>, K<sup>+</sup>-AT-Pases.<sup>26</sup> *C. nurvala* was reported to be effective in the prophylaxis of oxalate urolithiasis induced by simultaneous administration of sodium oxalate and methionine in guinea pigs.<sup>27</sup>

Studies on the stem juice of *M. paradisiaca* were found to be effective in dissolving the phosphate type of calculi in albino rats induced by the foreign-body insertion method using zinc discs.<sup>15</sup> In another experimental study stem juice of *Musa* significantly reduced the incidence of oxalate urolithiasis by lowering the activity of the enzyme glycolic acid oxidase.<sup>28</sup> The stem juice of *Musa* reduced urinary oxalate, glycolic acid, glyoxylic acid, and phosphorus excretion in hyperoxaluric rats.<sup>29</sup>

In the present study, the surface area or size of calculi was reduced by 33.04% in the active arm of group A, while an increase of 5.13% was noted in the placebo arm of that group ( $p = 0.017$ , unpaired  $t$ -test). In the active arm of group B, the surface area or size of calculi was reduced by 11.25%, while a 1.41% reduction was noted in the placebo arm of the group ( $p = 1.134$ , unpaired  $t$ -test). This result suggests statistically significant reduction in stone sizes. For the study as a whole, the result in the active arm, especially in small stone size ( $p = 0.017$ , unpaired  $t$ -test) is highly significant, despite a bias due to the small placebo arm.

As Ayurvedic drugs act slowly, a 3-month period is inadequate to gauge the effect of Herbmed, especially for large calculi. It is possible that the drug may work on specific types of calculi; in the small stone group some have shown complete expulsion ( $n = 5$ , 21.7%), and reduction ( $n = 11$ , 47.82%), while a few ( $n = 3$ , 13%) showed an increase in size. In the small calculi placebo arm of group A there was either reduction ( $n = 3$ , 37.5%) or increase in the stone size ( $n = 3$ , 37.5%). Further study with detailed metabolic analysis is required to predict which type of stone will respond more to Herbmed. The main drawbacks in the development of a standard drug may be the multicausal nature of urolithiasis, different biochemical disorders that lead to urolithiasis, and different chemical varieties of urolithiasis.

At the end of 3 months the VAS score and requirement of analgesics of both the active and placebo arms in both the groups was compared. In the active arm there was statistically significant lower VAS as compared to the placebo arm in the form of the highest VAS ( $p = 0.008$ , Mann-Whitney

test), average VAS ( $p = 0.001$ , chi-square test) and VAS at first episode of pain ( $p < 0.0001$ , Mann-Whitney test). The VAS scales of small and large stone sizes of both group A and B were comparable. This indicates that Herbmed also helps in reduction of pain, probably by facilitating the passage of fragments more easily. In the active arm the need for an analgesic (diclofenac) was significantly low ( $p < 0.0001$ , chi-square test) in both oral and injectable forms. Currently, surgical procedures and extracorporeal shock wave lithotripsy are commonly employed in the management of urinary calculus disease. The major drawback of these procedures is the possibility of recurrence of the calculi. Plant products and derivatives of their compounds as such may not completely replace these procedures but will surely help in decreasing the size of calculi as well as reduce the recurrence rate of renal calculi. Detailed biochemical evaluation will be taken up on the basis of this preliminary study.

## Conclusions

Our preliminary experience suggests that the ayurvedic formulation varuna and banana stem (Herbmed) shows promise for the management of upper urinary tract calculi, especially renal calculi. It helps to dissolve renal calculi and facilitate their passage, and reduces pain caused by renal and/or ureteric calculi. Herbmed has shown significant results in the group of patients with calculus size between 5 to 10 mm as compared with the placebo group; for larger calculi the preliminary result did not show significant results. A large phase III study with longer follow-up is required.

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