Original Article

Lycopodium clavatum for the management of urolithiasis: A randomised double blind placebo controlled trial

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Abstract

Background: Urolithiasis is the most common disease of urinary tract found worldwide. There are several approaches for the treatment of urolithiasis that include the use of various synthetic and natural drugs and/or surgery in the conventional system of medicine. **Objective:** This study was taken up to evaluate the efficacy of *Lycopodium clavatum* in the management of urolithiasis. **Materials and Methods:** A multicentric, randomised, double-blind, placebo-controlled trial was conducted. Patients having symptomatology like *Lycopodium clavatum* were enrolled after screening and repertorisation as per the inclusion and exclusion criteria. During acute renal colic, despite group allocation, the patients were either prescribed the indicated homoeopathic medicines or conventional medicine. The analysis was carried out with an intention-to-treat approach, and missing values were handled using Last Observation Carry Forward method. **Results:** There was no statistical significance between the groups ($P = 0.31$) in reference to the number of cases in which stones expelled during the trial. The mean size of single stone expelled was 9.4 ± 4.9 and 13.9 ± 2.2 in Verum and Placebo groups, respectively ($P = 0.12$). There was also no significant difference in the mean size of mean size of multiple stones; in Verum group (10.1 ± 5.3) and Placebo group (16.1 ± 9.1) ($P = 0.11$). For assessment of pain and dysuria, Visual Analogue Scale was used, and a statistically significant difference was found between the groups ($P = 0.039$) for pain, and positive trend for Homoeopathy was noted for dysuria. A verified symptom syndrome of *Lycopodium clavatum* has been observed. **Conclusion:** Future studies with pragmatic study design and individualistic Homoeopathy can be undertaken to assess the effectiveness of treatment in urolithiasis.

Keywords: Calculi, Colic, Homoeopathy, *Lycopodium clavatum*, Non-steroidal anti-inflammatory drug, Urolithiasis

Introduction

Humankind has been afflicted by urinary stones dating back to 4000 BC, and it is the most common disease of urinary tract.[1] Urolithiasis is a problem found worldwide in every culture, racial group and geographic location. The incidence and prevalence rates of kidney stones may be affected by genetic, nutritional and environmental factors.[2] Globally, the prevalence and recurrence rates of kidney stone disease are increasing, with limited options of effective drugs. Urolithiasis affects about 12% of the world population at some stage in their lifetime. In Indian population, about 12% of them are expected to have urinary stones, out of which, 50% may end up with loss of kidney functions.[1] In India, approximately 5–7 million patients suffer from kidney stone disease, and at least 1/1000 of the Indian population need hospitalisation due to kidney stone diseases.[3] In the geographical region of India, two distinct 'stone belts' have been identified: North India forms the 'First Stone' belt and parts of Maharashtra, Gujarat and Jabalpur in Madhya Pradesh form the 'Second Stone' belt.[4]

The symptoms of kidney stone are related to their location, whether it is in the kidney, ureter or urinary bladder. The signs

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and symptoms of the stone disease comprise renal colic, flank pain, haematuria, obstructive uropathy, urinary tract infections, blockage of urine flow and hydronephrosis. These conditions may result in nausea and vomiting with associated suffering from the stone event. Thus, the treatment and time lost from work involve substantial cost imposing an impact on the quality of life (QOL) and the nation's economy. Apart from these, kidney stones are associated with an increased risk of chronic kidney diseases, end-stage renal failure, cardiovascular diseases, diabetes and hypertension.[1]

There are several approaches for the treatment of urolithiasis that include the use of various synthetic and natural drugs in the conventional system of medicine. Once the presence of urinary stones is confirmed and their location, size and type are established, medical intervention comes into play that includes treatment by drug therapy or surgical removal of the stones. The intervention includes non-steroidal anti-inflammatory drugs (NSAIDs) and opioids for relieving pain associated with urolithiasis. Both the categories of drugs have been found to be equally effective although NSAIDs are known to cause potential gastrointestinal and renal side effects, whereas opioid analgesics require administration of antiemetic agents as they are known to cause nausea and vomiting along with urinary retention, constipation and respiratory depression. Medical expulsive therapy is used to allow spontaneous expulsion of moderately sized distal ureteral calculi from the urinary tract. Similarly, there are different groups of drugs for different types of calculi with their potential side effects or limitations. Apart from the administration of drugs to prevent the formation and/or expulsion of the renal stones, the other approaches depending on the case are extracorporeal shock wave lithotripsy, ureteroscopy, percutaneous nephrolithotomy, laparoscopic surgery and open surgery.[5(i)] The limitations in the conventional system of medicine for treating this condition are the cost involved in the diagnosis with regard to the type of stone, metabolic disorder, invasive procedures and side effects of the medicines.[5(ii)]

According to a survey conducted in India, 62% of the current Homoeopathy users have never tried conventional medicines for day-to-day health problems and 82% would not switch to conventional treatments, unless it is an emergency. Presently, Homoeopathy is accepted as a system of gentle healing. The inherent strength of the system makes it a safe therapy, eco friendly and free from adverse side effects.[6] A retrospective study on the prevalence and likelihood ratio of symptoms in patients with good therapeutic response to *Lycopodium clavatum* also reflects the action of this drug on kidney stones.[7] Homoeopathic literature shows the usefulness of homoeopathic medicines in the expulsion and dissolution of renal stones. There are case reports reflecting the importance of individualisation and the effectiveness of homoeopathic medicines in the expulsion of renal stones.[8-11]

Another study, a preliminary investigation on ultra-high diluted *Berberis vulgaris* in experimental urolithiasis, showed that the root-bark of homoeopathic medicine *Berberis vulgaris* has strong anti-urolithiasis potential at ultra-diluted dose.[12] Another *in vitro* study conducted using homoeopathic medicine signifies *Berberis vulgaris* to be a potent drug against calcium oxalate crystallisation both at the level of nucleation and aggregation.[3]

The Central Council for Research in Homoeopathy conducted a multicentric observational study to evaluate the effectiveness of Homoeopathy in urolithiasis, which showed positive results. The medicines found most useful were *Lycopodium clavatum* in 40.9% (n = 90) of cases; *Sulphur* in 12.3% (n = 27) of cases; *Pulsatilla nigricans* in 8.2% (n = 18) of cases; *Nux vomica* in 6.2% (n = 14) of cases and *Cantharis vesicatoria* in 5.9% (n = 13) of cases.[13]

With this background and keeping in view the results of a previous study, this double-blind, placebo-controlled study has been undertaken by the Council to evaluate the efficacy of *Lycopodium clavatum* in the treatment of urolithiasis and to access the effectiveness of homoeopathic medicines in the treatment of acute renal colic. Further, the symptoms of *Lycopodium clavatum* medicine were also verified.

Materials and Methods

Study design, setting and duration

This multicentric, randomised, double-blind, placebo-controlled trial was conducted at seven centres, namely the Central Research Institute (H), Noida (Uttar Pradesh); the Homoeopathic Drug Research Institute, Lucknow (Uttar Pradesh); the Regional Research Institute (H), Shimla (Himachal Pradesh), Jaipur (Rajasthan) and Puri (Odisha); Dr. Anjali Chatterjee Regional Research Institute (H), Kolkata (West Bengal) and the Clinical Research Unit (H), Siliguri (West Bengal), between July 2012 and March 2015. The four study sites in the first stone belt and three study sites in the northeast region were considered keeping in view the prevalence of the disease condition as per the two belts mentioned in the introduction section. The investigators were given training on the study protocol before the initiation of the study. The data of cases wherein *Lycopodium clavatum* was prescribed in the observational study of Council[13] were investigated, and symptom syndrome was framed subsequently and provided to the study investigators as ready reference before initiating this study.

The study protocol and procedure followed were in accordance with ethical standards of Council, Helsinki Declaration of 1964[14] for human experimentation, revised in October 2000 and with Good Clinical Practice in India.[15] Data of trial were reported as per the Reporting Data on Homoeopathy Treatments Guidelines.[16]

Protocol clearance was obtained from the Institutional Ethic Committee of the Council and registered with the Clinical Trials Registry of India with trial registration no. CTRI/2011/12/002210 dated 8.12.2011. Written informed consent for participation in study and use of patient data

for research and educational purposes was obtained from participants before enrollment in the study.

Eligibility criteria

Screening

During the enrolment period of the study, patients reporting at the outpatient department (OPD) of the seven research centres were screened (preliminary and detailed) on the basis of the inclusion and exclusion criteria. Patients having symptomatology like *Lycopodium clavatum* after repertorisation were enrolled in the study by Investigator without deviating from the homoeopathic principle of 'Individualisation'. Each participant was verbally explained about the study, with the help of a patient information sheet, and thereafter, a written informed consent was obtained from them for voluntary participation in the study. However, they were free to withdraw the consent from the study at any point of time.

Inclusion criteria

a. Cases with radiographic evidence (X-ray and ultrasound of kidney/ureter/bladder [KUB]) of calculi in KUB (both symptomatically and asymptomatically diagnosed cases) with or without mild hydronephrosis
b. Size of calculi: In the case of single calculus, 5 mm or above
c. In the case of two or more calculi, one calculus must be 5 mm or above
d. Both sexes of age between 18 and 60 years
e. Written informed consent from the patient.

Exclusion criteria

a. Cases with moderate/severe hydronephrosis
b. Creatinine levels >2 mg%
c. Recurrent urinary tract infections
d. Acute retention of urine for >24 hours
e. Cases with hyperparathyroidism
f. Cases with gross developmental defects or structural abnormality of kidney
g. Cases with other systemic diseases such as cardiovascular and endocrinal diseases or systemic infections or on other treatment therapies
h. Impacted calculus, staghorn calculus
i. Cases not having *Lycopodium clavatum* symptomatology
j. If any exclusion criteria develop during the study, the case will be excluded.

Randomisation and group allocation

Patients fulfilling the eligibility criteria were enrolled and randomised into two groups – verum i.e., *Lycopodium clavatum,* and placebo group. The allocation in the respective groups was as per random numbers generated with the help of computer-based software available at www.randomizer.org (last accessed on 12 June 2012). Randomization chart was generated by statistician involved in study. They received either of the intervention i.e., *Lycopodium clavatum* or placebo (1:1 ratio).

As this is a multicentric study, the medicine and placebo were prepared in four lots i.e., A, B, C and D, which were sent to all the centres. Two lots belonged to verum and two belonged to placebo groups. This was done to reduce the bias to the extent possible among the site investigators.

Blinding

Both groups were assessed on same parameters. Participants and Investigator were blinded during the study period. Concealment was assured as the pharmacist had dispensed medicine to the patients from lots A, B, C and D as per the medicine lot assignment envelop provided by the Council. Pharmacist's contact with the patient was limited to dispensing and instruction regarding the administration of medicine. His/her contact with the investigator was limited to the communication of the identity of the patient and the medicine to be prescribed. The investigator was not aware to which group and to which medicine lot the patient had been assigned.

Unblinding of the study was to be done only after the study got completed at all the centres, except in the case of reporting of any adverse event.

Intervention

History of each individual case was recorded on a structured pro forma followed by analysis and evaluation of the symptoms; totality of the symptoms was formed and repertorised using Synthesis repertory is printed version of Software program RADAR. Archibel, a Zeus Soft company at Belgian manufacturer Rapid Aid to Drug Aimed Research (RADAR). Patients those who were fitting to *Lycopodium clavatum* drug picture were enrolled in the study, and others were treated in the OPD. As per the randomisation chart, the patients were allocated to any one of the four medicine lots, two lots each contained either *Lycopodium clavatum* or placebo.

The potency was selected as per the susceptibility of the patient and followed serially by next higher potency as per the need of the case. A single dose was prescribed in each case, and medicine was repeated depending on the intensity of the complaints. The patients were advised to report for follow-up as per the need. The patients were followed up at one-month interval, and case was assessed for the respective symptoms for example, pain and dysuria by the investigator. Repetition of the medicine was done in the same or higher potency as per the need.

During acute renal colic, despite group allocation, the patients were prescribed the indicated homoeopathic medicines, and if not managed by Homoeopathy, they were either referred to the consultant or were left free to take any medication for acute phase. This information was also recorded. After the completion of acute episode, they received medicine from the allocated group of treatments till completion of 1 year, and then data were analysed.

Sample size

The sample size was calculated keeping in view the outcome of the earlier observational study on urolithiasis conducted by

the Council (2005–2010).[13] The effect size in the previous study was 0.5, so in the present study also, using an effect size of 0.5 with the power 0.85, $\alpha = 0.05$ and intervention:placebo at 1:1, the sample size was calculated as 59:59. Thus, a total of 118 cases were required for the final analysis. It was considered that there might be an estimated 25% of dropouts, and few of the cases may have an acute phase and will be then considered as a subgroup, and hence the total sample size should be 180. Thus, cases to be enrolled at each centre were 15:15 (verum: placebo).

Outcome measures

The primary outcome measure was clinical cure i.e., dissolution/expulsion of renal calculus with radiological evidence (X-ray and ultrasound KUB) of no calculus in the urinary tract. Each patient enrolled in the study was assessed with laboratory parameters at every 3rd, 6th, 9th and 12th month. If patients reported of any expulsion in between the follow-up, ultrasound examination was done to assess.

The secondary outcome parameters were relief in pain (flank) and dysuria as per the Visual Analogue Scale (VAS) from 0 to 10, where 0 indicates no pain and 10 indicates maximum severity, assessed at every month follow-up. The World Health Organization-QOL (WHO-QOL) BREF was assessed at baseline and at 12 months for changes in QOL parameters.

Statistical analysis

The analysis was carried out with intention-to-treat (ITT) approach, and missing values were handled using Last Observation Carry Forward (LOCF) method. IBM at Bengaluru, India manufactured Statistical Package for Social Sciences (SPSS) software, version 20 was used for carrying out the statistical analysis. Comparison between verum and placebo groups was performed at baseline to assess randomisation effect using an independent *t*-test for continuous variables and Chi-square test for ordinal data as applicable. Repeated-measures ANOVA was applied to assess the difference between the groups at different time points. Primary and Secondary outcome measures were assessed using Chi square test and independent *t*-test respectively. In all the analyses, $P < 0.05$ was considered statistically significant.

Results

Sociodemographic characteristics

Between July 2012 and March 2015, a total of 753 patients were screened, and 134 patients were enrolled from seven different institutes/units of the Council located all over India. Out of these 753 screened cases, 619 were excluded due to various reasons as reflected in Figure 1. Due to difficulties in achieving the sample size, an interim analysis of the study was performed, and it was decided by the regulatory committees (Special Committee of Clinical Research and Scientific Advisory Committee of the Council) to stop the enrolment of patients and complete the follow-up of enrolled cases. Finally, 134 patients, 63 in Verum group and 71 in Placebo group, were considered for primary outcome analysis. Baseline characteristics were similar for both groups. The

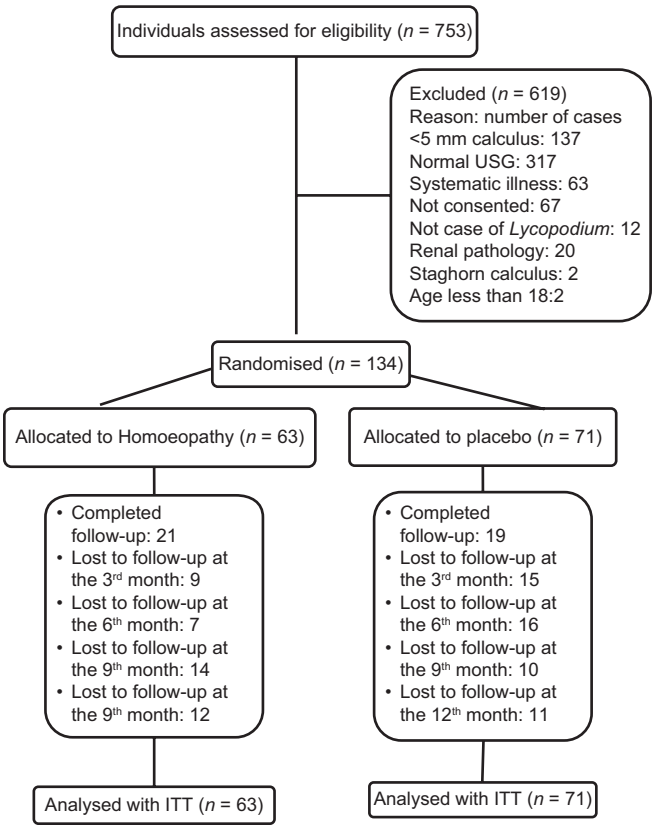

Figure 1: Study flowchart

mean age of the patients was 35.8 ± 11.6 years in the Verum group and 35.5 ± 11.9 years in the Placebo group. A total of 47 (74.6%) patients and 52 (73.2%) patients were male and 16 (25.4%) patients and 19 (26.8%) patients were female in each respective group. The duration of illness i.e., urolithiasis, was 1.7 ± 3.5 years in Verum group and 1.4 ± 2.8 years in Placebo group. Other demographic details are summarised in Table 1.

At baseline, 36 (57.1%) patients in the Verum group and 32 (45.1%) patients in the Placebo group had single stone with a mean size of 8.3 ± 3.8 mm and 9.4 ± 6.7 mm, respectively. Right-sided kidney stones were present in 15 (23.8%) patients of the Verum group and 21 (29.6%) patients in the Placebo group; while bilateral stones were present in 19 (30.2%) patients of the verum group and 17 (23.9%) patients of the Placebo group. Other stone-related details such as stone size and location-wise size are described in Table 2.

Efficacy results: Intention-to-treat analysis

The results were assessed after completion of 1-year follow-up, and ITT analysis was considered as in few cases the stone got expelled/dissolved before 1 year and others were dropped out due to various reasons. Thus, LOCF was considered for all the 134 cases enrolled in the study.

Stone was expelled in 12 (19.0%) cases in the Verum group and in 9 (12.7%) cases in the Placebo group. No significant difference was found between the groups. The mean size of

Table 1: Comparison of demographic characteristic of verum and placebo groups at baseline

Variables	Verum (*n*=63)	Placebo (*n*=71)	*P*
Age	35.8±11.6	35.5±11.9	0.85*
Sex			
Male	47 (74.6)	52 (73.2)	0.85£
Female	16 (25.4)	19 (26.8)	
Duration of diseases (years)	1.7±3.5	1.4±2.8	0.55*
Economic status			
Lower	30 (47.6)	31 (43.7)	0.96£
Middle	26 (41.3)	31 (43.7)	
Upper	2 (3.2)	2 (2.8)	
Not specified	5 (7.9)	7 (9.9)	
Food habit			
Vegetarian	30 (47.6)	34 (47.9)	0.53£
Non-vegetarian	27 (42.9)	26 (36.6)	
Not specified	6 (9.5)	11 (15.5)	
Occupation			
Government employee	1 (1.6)	1 (1.4)	0.33£
Private	20 (31.9)	19 (26.8)	
Professional	5 (7.9)	8 (11.3)	
Labours	14 (22.2)	10 (14.1)	
Homemaker	16 (25.4)	15 (21.1)	
Not specified	7 (11.1)	18 (25.4)	
History of addiction			
Alcohol	3 (4.8)	1 (1.4)	0.38£
Smoking	7 (11.1)	5 (7.0)	
Tobacco chewing	7 (11.1)	9 (12.7)	
Smoking + alcohol	1 (1.6)	2 (2.8)	
Tobacco chewing + smoking	2 (3.2)	0	
Tobacco chewing + smoking + alcohol	0	2 (2.8)	
Nil	31 (49.2)	31 (43.7)	
Not specified	12 (19.0)	23 (32.4)	
Pain	4.8±2.3	5.1±2.2	0.48*
Dysuria	2.8±2.8	3.0±3.0	0.75*
Haematuria	47 (74.6)	56 (78.9)	0.74£
Microscopic haematuria	11 (17.5)	10 (14.1)	
Gross haematuria	5 (7.9)	4 (5.6)	

*Independent *t*-test used, £Pearson's Chi-squared test used

single stone expelled in the Verum group was 9.4 ± 4.9 mm and 13.9 ± 2.2 mm in the Placebo group; the mean size of multiple stone was 10.1 ± 5.3 mm in the Verum group and 16.1 ± 9.1 mm in the Placebo group, which was not found to be statistically significant ($P = 0.12$ and $P = 0.11$) respectively. Although there was no statistical difference in the size of stone expelled and number of stones (single/multiple) expelled in the Verum and Placebo groups, patients reported symptomatic relief. Details of outcome assessment results are summarised in Table 3. The WHO-QOL Bref was used for the assessment of QOL; no difference was found between the groups [Table 3]. For the assessment of pain and dysuria, VAS was used, and statistically significant difference ($P = 0.039$) was found between the two groups for pain at different time points [Figure 2]. The positive trend in favour of Homoeopathy was found in dysuria [Figure 3]. For acute pain management, patients were advised to take their desired intervention, and the events were recorded. A total of 15 patients were recorded for acute pain: nine patients were from the Verum group and six were from the Placebo group. Eight of the 15 patients were prescribed homoeopathic intervention such as *Belladonna* and *Magnesia phosphorica* and seven were managed by conventional medicine.

Verified *Lycopodium clavatum* symptoms

To achieve the secondary objective of the study, *Lycopodium clavatum* symptoms for all the 63 cases in the Verum group were assessed in relation to medicine-specific symptoms found in the observation study of urolithiasis conducted by the Council[13] and for the prevalence and likelihood ratio of *Lycopodium clavatum* symptoms' study.[7]

The symptom syndrome of *Lycopodium clavatum* confirmed in this study is mentioned in Table 4.

Discussion

This was a double-blind, randomised, placebo-controlled study, and the physician was to prescribe *Lycopodium clavatum* on the basis of individualisation. These patients not covering the symptomatology of *Lycopodium clavatum* were excluded from the study and were treated in the general OPD. Enrolment in the study was difficult as many cases, though reflecting *Lycopodium clavatum* symptomatology, were excluded as the size of the renal calculus was <5 mm, which can be seen from the large gap in the screened ($n = 753$) and enrolled ($n = 134$) cases. Strict eligibility criteria affected the enrollment and further affected the external validity of study.

There was a heavy loss to follow-up during the study period, which made assessment of results tough. Another limitation was that after selecting *Lycopodium clavatum* as medicine for patients at baseline, the investigators were supposed to continue the same medicine with suitable potencies during follow-up period, which contradicts the routine homoeopathic practice where there could be requirement of change in prescription. It was observed in one of the reviews that, often, homoeopaths do not find the correct remedy at once and/or change the remedy as the clinical picture changes. In a case of a double blind trial, a homoeopathic practitioner often encounters the challenge that, changes occuring due to any three possibilities, namely, a failure to reach correct similimum, any symptom shift in patients, totality or patient being a participants of a placebo group.[17] Thus, physician bias to enroll non-*Lycopodium clavatum* cases in this study cannot be ruled out.

In an observational study of the Council[13] on urolithiasis, there was expulsion of stone in 41% of cases, whereas in the present study, stone was expelled in only 19% of cases. The difference in the results could be because of the study design. In the observational study, though the prescription was individualised, there was freedom to the investigators for change of prescription or potency of medicine. This was not applicable in the current study. In the present study, double-blind, placebo-controlled methodology was adapted,

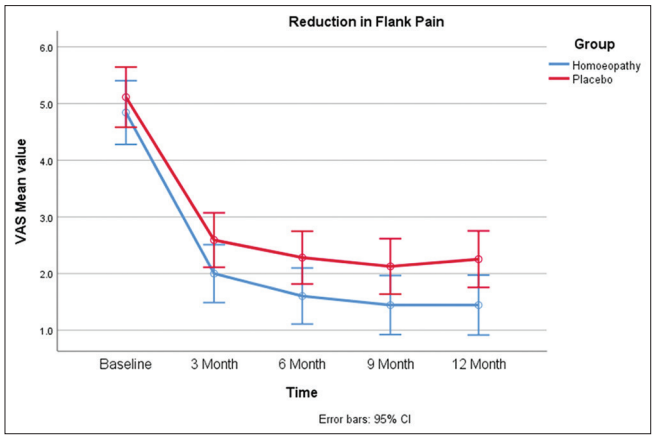

Figure 2: Reduction in flank pain at different time points

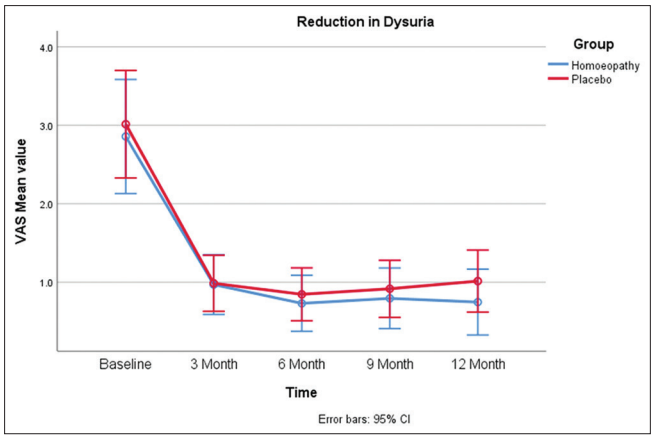

Figure 3: Reduction in dysuria at different time points

Table 2: Comparison related to number of stones, position, location and size of verum and placebo groups at baseline

Variables	Verum (*n*=63)	Placebo (*n*=71)	*P*
No. of cases with stone			
Single	36 (57.1)	32 (45.1)	0.16£
Multiple	27 (42.9)	39 (54.9)	
Position of stone			
Right kidney	15 (23.8)	21 (29.6)	0.64
Left kidney	19 (30.2)	21 (29.6)	
Right + left kidney	19 (30.2)	17 (23.9)	
Not specified	10 (15.9)	14 (19.7)	
Location of stone			
Calyx	43 (68.3)	43 (60.6)	0.37£
Pelvis	2 (3.2)	1 (1.4)	
Ureteric	2 (3.2)	2 (2.8)	
Lower ureteric	6 (9.5)	5 (7.0)	
Middle ureteric	0	3 (4.2)	
Upper ureteric	3 (4.8)	1 (1.4)	
Base bladder	0	1 (1.4)	
Calyx + pelvis	1 (1.6)	3 (4.2)	
Calyx + ureteric	1 (1.6)	0	
Calyx + lower ureteric	3 (4.8)	7 (9.9)	
Calyx + middle ureteric	2 (3.2)	1 (1.4)	
Calyx + upper ureteric	0	3 (4.2)	
Calyx + lower ureteric + middle ureteric	0	1 (1.4)	
Size of stone (mm)			
Single stone	8.3±3.8	9.4±6.7	0.39*
Multiple stone	14.6±9.9	16.4±8.7	0.43*
Size of stone with respect to location			
Calyces	7.2±3.0	7.4±4.5	0.80*
Pelvis	18.0±5.2	9.0±6.7	0.11*
Pelvic ureteric	15.5±2.5	15.0±9.9	0.93*
Lower ureteric	6.5±2.1	6.9±2.9	0.69*
Middle ureteric	10.6±1.4	14.5±9.2	0.60*
Upper ureteric	8.4±1.2	10.7±4.6	0.45*
WHO-QOL domains			
Physical	57.3±8.7	55.7±9.0	
Psychological	54.8±12.4	56.5±13.2	0.30*
Social	63.8±16.5	58.3±16.6	0.05*
Environmental	57.1±12.2	57.1±11.4	0.98*

*Independent *t*-test used, £Pearson's Chi-squared test used. WHO-QOL: World Health Organization-Quality of Life

Table 3: Comparison of outcome measures between verum and placebo groups

	Verum (*n*=63)	Placebo (*n*=71)	*P*
Primary outcome measure			
Expulsion of stone (number of cases)			
Total number of stones expelled (%)	12 (19.0)	9 (12.7)	0.31[£]
Within 6 months	9	3	0.48
Within 12 months	3	6	0.56
Not expelled	51	62	
Number of stones expelled			
Single	9	5	0.33[£]
Multiple	3	4	
Size of stones expelled (mm)			
Single	9.4±4.9	13.9±2.2	0.12*
Multiple	10.1±5.3	16.1±9.1	0.11*
Secondary outcome measure			
WHO-QOL domains			
Physical	57.3±8.6	58.1±7.5	0.74*
Psychological	58.8±11.3	59.1±12.6	0.93*
Social	66.7±9.6	63.7±11.7	0.41*
Environmental	62.9±11.4	60.0±10.4	0.37*

*Independent *t*-test used, [£]Pearson's Chi-squared test used. WHO-QOL: World Health Organization-Quality of Life

Table 4: Verified symptoms of *Lycopodium clavatum* (verum group)

Symptoms	*n* (%)
Urinary stone history*	63 (100)
Sweet desire*	9 (14.29)
Distension of abdomen/flatulence*	18 (28.57)
Irritability/getting anger easily*	9 (14.29)
Contradiction intolerance*	8 (12.70)
Constipation*	10 (15.87)
Lack of vital heat*	9 (14.29)
Want of self-confidence*	4 (6.35)
Desire for warm food	15 (23.81)
Desire company	12 (19.05)
Aversion to company	7 (11.11)
Decreased appetite/easy satiety	5 (7.94)

*Confirmatory symptoms

which is the gold standard in conventional medicine for clinical trials, but it seems that, this methodology may not be suitable for Homoeopathy practice, which is reflected in other homoeopathic studies.[18,19]

This observation has been in consonance with a study where the impact of study quality on outcome in placebo-controlled trials of Homoeopathy was assessed, and it was found that studies with better methodological quality tended to yield less positive results.[20]

In the present study, significant reduction in flank pain and pain during micturition was found between the groups at different time points. This is in agreement with another homoeopathic pilot study on urolithiasis.[21]

In the present study, 12 symptoms of *Lycopodium clavatum* were found in accordance with a previous study of the Council,[13] and eight symptoms were confirmatory as per the study of the prevalence and likelihood ratio of *Lycopodium clavatum* symptoms' study.[7] Thus, these symptoms can be considered while prescribing *Lycopodium clavatum* in any disease condition. Digestive troubles and urinary complaints were present in almost all the cases of urolithiasis.

Patients in the placebo group had undergone the homoeopathic case history recording procedure that might contribute considerably to a possible treatment effect, decreasing the likelihood of identifying differences between the groups.[20] To achieve efficacy results using *Lycopodium clavatum* in urolithiasis, a pragmatic approach is suggested for future studies.

Conclusion

In the present study setting, Homoeopathy medicine *Lycopodium clavatum* did not show significant results in expulsion/dissolution of the renal calculi in comparison with placebo. Thus, the need of rigorous methodology of trial, external validity and application of single medicine in the treatment of such conditions where acute episodes and change in symptomatology are expected, should be thought of. The significant difference in the flank pain and positive trend in dysuria in favour of Homoeopathy are encouraging, and future studies with pragmatic study design and individualistic Homoeopathy can be undertaken to assess the effectiveness of *Lycopodium clavatum* in the treatment of urolithiasis. Moreover, this study may help to frame a strategic plan for treatment of such cases.

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Conflicts of interest

None declared.

References

1. Alelign T, Petros B. Kidney stone disease: An update on current concepts. Adv Urol 2018;3068365.
2. Niemann T, Kollmann T, Bongartz G. Diagnostic performance of low-dose CT for the detection of urolithiasis: A meta-analysis. AJR Am J Roentgenol 2008;191:396-401.
3. Ganesan T, Ravi DB, Vasavan J, Khurana A, Nayak D, Periandavan K. Homoeopathic preparation of *Berberis vulgaris* as an inhibitor of calcium oxalate crystallization: An *in vitro* evidence. Indian J Res Homeopathy 2015;9:152-7.
4. Talati J, Tiselius H, Albala DM, Ye Z. Epidemiology of stone diseases in Northern India. In: Urolithiasis: Basic Science and Clinical Practice. London: Springer; 2012.

5(i). Bawari S, Sah AN, Tewari D. Urolithiasis: An update on diagnostic modalities and treatment protocols. Indian J Pharm Sci 2017;79:164-74.

5(ii). A C Neilsen survey backs homeopathy benefits. Business Standard. 2007. Available from: http://www.business-standard.com/india/news/a-c-nielsen-survey-backs-homeopathy-benefits/295891/. [Last accessed on 2019 Sep 23].

6. Central Council for Research in Homoeopathy. Dossier: Science of Gentle Healing. New Delhi: Central Council for Research in Homoeopathy; 2018.
7. Eizayaga JE, Pozzi MI, Canan MC, Saravia L. Prevalence and likelihood ratio of symptoms in patients with good therapeutic response to *Lycopodium clavatum*. A retrospective study. Homeopathy 2016;105:78-83.
8. Gupta AK, Gupta J, Siddiqui VA, Mishra A. A big urinary calculus expelled with homoeopathic medicine. Indian J Res Homoeopathy 2008;2:50-5.
9. Sumithran PP. A case of multiple urinary calculi. Indian J Res Homoeopathy 2016;10:142-9.
10. Chakma A. Renal calculi: Evidence based case study. RA J Appl Res 2015;1:227-34.
11. Hati AK, Rath S, Nayak C, Raj I, Sahoo AR, Paital B. Successful treatment of ureteric calculi with constitutional homoeopathic medicine *Lycopodium clavatum*: A case report. J Drug Deliv Ther 2018;8:1-7.
12. Jyothilakshmi V, Thellamudhu G, Kumar A, Khurana A, Nayak D, Kalaiselvi P. Preliminary investigation on ultra high diluted *B. vulgaris* in experimental urolithiasis. Homeopathy 2013;102:172-8.
13. Siddiqui VA, Singh H, Gupta J, Nayak C, Singh V, Sinha MN, *et al*. A multicentre observational study to ascertain the role of homoeopathic therapy in urolithiasis. Indian J Res Homoeopath 2011;5:30-9.
14. World Medical Association. Declaration of Helsinki ethical principles for medical research involving human subjects. Bull World Health Organ 2001;79:373-74.
15. EMEA-European Medicine Agency. Guidelines for Good Clinical Practice, ICH topic E6 (R1): EMEA-European Medicine Agency; CPMP/ICH/135/95.
16. Dean ME, Coulter MK, Fisher P, Jobst KA, Walach H. Reporting data on homeopathic treatments (RedHot): A supplement to CONSORT. J Altern Complement Med 2007;13:19-23.
17. Linde K, Melchart D. Randomized controlled trials of individualized homeopathy: A state-of-the-art review. J Altern Complement Med 1998;4:371-88.
18. Shipley M, Berry H, Broster G, Jenkins M, Clover A, Williams I. Controlled trial of homoeopathic treatment of osteoarthritis. Lancet 1983;1:97-8.
19. Fisher P, Greenwood A, Huskisson EC, Turner P, Belon P. Effect of homeopathic treatment on fibrositis (primary fibromyalgia) BMJ 1989;299:365-6.
20. Linde K, Scholz M, Ramirez G, Clausius N, Melchart D, Jonas WB. Impact of study quality on outcome in placebo-controlled trials of homeopathy. J Clin Epidemiol 1999;52:631-6.
21. Gupta G. Evidence Based Pilot Study on Role of Homoeopathic Drugs in Cases of Kidney Stone, 18th AHML, International Conference, Kuala Lumpur; 2009.

युरोलिथिएसिस के प्रबंधन के लिए लाइकोपोडियम क्लैवेटमः एक यादृच्छिक प्लासिबो नियंत्रित परीक्षण

पृष्ठभूमि : यूरोलिथिएसिस दुनिया भर में मूत्र मार्ग का सबसे आम रोग है। पारंपरिक उपचार में विभिन्न कृत्रिम और प्राकृतिक दवाएं और/या सर्जरी ही पर्याय हैं। होम्योपैथिक साहित्य में मूत्र मार्ग की पत्थरी के निकलने और टूटने के लिए होम्योपैथिक औषधियों की ओर इंगित करता है।

उद्देश्य : मूत्रमार्ग में पथरी के उपचार में *लाइकोपोडियम क्लैवेटम* की प्रभावकारिता का मूल्यांकन करना।

कार्यप्रणाली : एक बहुस्तरीय, यादृच्छिक, दोहरा अंध कूट–भेषज नियंत्रित परीक्षण किया गया। मरीजों को शामिल और बहिष्कार किए जाने के मापदंड के अनुसार जांच की गई और उन मामलों में जहां पुनर्नियोजन के बाद *लाइकोपोडियम क्लैवेटम* औषधियों की ओर इंगित किया गया था, उनका नामांकन किया गया। गुर्दों में अत्याधिक दर्द के दौरान, समूह आबंटन के बावजूद, रोगियों को या तो निर्दिष्ट होम्योपैथिक दवाओं या पारंपरिक चिकित्सा का संकेत दिया गया था, दृश्य अनुरुप मापक (वीएएस) का उपयोग करके दर्द और पेशाब में जलन का मूल्यांकन किया गया।

परिणाम : उन मामलों की संख्या के लिए समूहों को कोई सांख्यिकीय महत्वपूर्ण (p = 0.31) नहीं था, जिनमें परीक्षण के दौरान पत्थरी को बाहर निकाल दिया गया था। होम्योपैथी समूह में बाहर निकली एकल पत्थरी का औसत आकार 9.4 मिमी., 4.9 मिमी. और कूट भेषज समूह 13.9 मिमी., 2.2 मिमी था ; होम्योपैथी समूह में एकाधिक पत्थर 10.1 मिमी., 5.3 मिमी. और कूट भेषज समूह में 16.1 मिमी., 9.1 मिमी. था जो क्रमशः सांख्यिकीय महत्वपूर्ण (p = 0.12 और p = 0.11) नहीं पाया गया था। दर्द के लिए समूहों (p = 0.039) के बीच वीएएस स्कोर में महत्वपूर्ण अंतर पाया और होम्योपैथी के लिए सकारात्मक प्रवृत्ति पेशाब में दर्द के लिए नोट की गई। *लाइकोपोडियम क्लेवेट्म* का एक सत्यापित संलक्षण समूह निर्दिष्ट हुआ है।

निष्कर्ष : होम्योपैथिक उपचार की प्रभावशीलता का आंकलन करने के लिए भविष्य के अध्ययन को व्यावहारिक अध्ययन योजना और व्यक्तिगत होम्योपैथी के साथ किया जा सकता है।

Le *Lycopodium clavatum* pour le traitement de l'urolithiase : Un essai contrôlé randomisé en double aveugle contre placebo

Contexte: La lithiase urinaire est la maladie la plus courante des voies urinaires dans le monde. Le traitement conventionnel comprend divers médicaments synthétiques et naturels et / ou une intervention chirurgicale. La littérature homéopathique montre l'efficacité des médicaments homéopathiques pour l'expulsion et la dissolution des calculs.

Objectifs: Evaluer l'efficacité du *Lycopodium clavatum* dans le traitement de la lithiase urinaire et en vérifier les symptômes ; accéder à l'efficacité des médicaments homéopathiques dans le traitement de la colique rénale aiguë.

Méthodologie: Un essai randomisé multicentrique, en double insu et contrôlé par placebo a été mené. Les patients ont été sélectionnés en fonction des critères d'inclusion et d'exclusion et seuls les cas pour lesquels le Lycopodium clavatum était indiqué après avoir été répertoriés ont été retenus. Au cours de coliques néphrétiques aiguës, malgré l'affectation des groupes, des médicaments homéopathiques indiqués ou des médicaments conventionnels ont été prescrits aux patients ; la douleur et la dysurie ont été évaluées à l'aide de l'échelle visuelle analogique (EVA).

Résultats: Il n'y avait pas de différence statistiquement significative ($P = 0,31$) entre les groupes en ce qui concerne le nombre de cas d'expulsion de calculs au cours de l'essai. La taille moyenne du calcul unique expulsé dans le groupe homéopathie était de 9,4 mm ± 4,9 mm et de 13,9 mm ± 2,2 mm dans le groupe placebo la taille des calculs multiples était de 10,1 mm ± 5,3 mm dans le groupe homéopathie et de 16,1 mm ± 9,1 mm dans le groupe placebo, ce qui n'était pas statistiquement significatif ($P = 0,12$ et $P = 0,11$) respectivement. Une différence significative a été trouvée dans le score EVA entre les groupes ($P = 0,039$) pour la douleur et une tendance positive pour l'homéopathie a été notée pour la dysurie. Un syndrome symptomatique et vérifié du Lycopodium a été observé.

Conclusion: De futures études peuvent être entreprises avec une conception d'étude pragmatique et une homéopathie individualisée pour évaluer l'efficacité du traitement homéopathique.

Lycopodium clavatum para el tratamiento de la urolitiasis: Un ensayo aleatorizado doble ciego controlado con placebo

Fundamentos: La urolitiasis es la afección más común del tracto urinario en todo el mundo. El tratamiento convencional incluye diferentes fármacos sintéticos y naturales y/o cirugía. La bibliografía homeopática muestra la utilidad de los medicamentos homeopáticos en expulsar y disolver los cálculos.

Objetivos: Evaluación de la eficacia de *Lycopodium clavatum* en el tratamiento de la urolitiasis, así como la verificación de sus síntomas y acceder a la eficacia de los medicamentos homeopáticos en el tratamiento del cólico renal agudo.

Metodología: Se realizó un ensayo aleatorizado multicéntrico a doble ciego y controlado con placebo. Los pacientes fueron estudiados en función de los criterios de selección y exclusión, e incluidos en el ensayo si quedaba indicado *Lycopodium clavatum* tras la repertorización. Durante el cólico renal agudo, pese a la asignación a un grupo, los pacientes recibieron los medicamentos homeopáticos indicados o un fármaco convencional; el dolor y la disuria se evaluaron con la escala VAS (*Visual Analogue Scale*).

Resultados: No se observaron diferencias estadísticamente significativas ($P = 0,31$) entre los grupos en cuanto al número de casos en los que se expulsó el cálculo durante el ensayo. El tamaño medio de los cálculos únicos expulsados en el grupo de homeopatía fue de 9,4 mm ± 4,9 mm y, en el grupo con placebo, de 13,9 mm ± 2,2m. En el caso de cálculos múltiples, el tamaño medio fue de 10,1 mm ± 5,3 mm en el grupo homeopático y de 16,1 mm ± 9,1 mm en el grupo con placebo; las diferencias no fueron estadísticamente significativas ($P = 0,12$ y $P = 0,11$) respectivamente. Se observe una diferencia significativa en la puntuación VAS entre los grupos ($P = 0,039$) en cuanto al dolor, así como una tendencia positiva hacia la homeopatía en cuanto a la disuria. Se ha observado un síndrome de síntoma verificado de Lycopodium.

Conclusiones: Se pueden realizar estudios futuros con un diseño de estudio pragmático y homeopatía individualizada para evaluar la eficacia del tratamiento homeopático.

Lycopodium clavatum zur Behandlung von Urolithiasis: Eine randomisierte doppelblinde, placebokontrollierte Studie

Hintergrund: Die Urolithiasis ist die weltweit häufigste Erkrankung der Harnwege. Die konventionelle Behandlung umfasst verschiedene synthetische und natürliche Medikamente und / oder Operationen. Die homöopathische Literatur zeigt die Nützlichkeit homöopathischer Arzneimittel zum Ausstoßen und Auflösen von Steinen.

Ziel: Bewertung der Wirksamkeit von Lycopodium clavatum bei der Behandlung von Urolithiasis und Überprüfung seiner Symptome sowie Zugang zur Wirksamkeit homöopathischer Arzneimittel bei der Behandlung von akuter Nierenkolik.

Methodik: Eine multizentrische, randomisierte, doppelblinde, placebokontrollierte Studie wurde durchgeführt. Die Patienten wurden nach den Einschluss- und Ausschlusskriterien gescreent und in den Fällen, in denen Lycopodium clavatum nach der Repertorisierung angezeigt war, eingeschlossen. Während einer akuten Nierenkolik wurden den Patienten trotz Gruppenzuordnung entweder indizierte homöopathische Arzneimittel oder konventionelle Medikamente verschrieben; Schmerz und Dysurie werden mit der Visual Analogue Scale (VAS) bewertet.

Ergebnisse: Es gab keinen statistisch signifikanten Unterschied ($P = 0,31$) zwischen den Gruppen für die Anzahl der Fälle, in denen Steine während des Versuchs ausgetrieben wurden. Die mittlere Größe eines in der Homöopathie-Gruppe ausgestoßenen Einzelsteins betrug 9,4 mm ± 4,9 mm und 13,9 mm ± 2,2 mm in der Placebo-Gruppe; multiple stone betrug in der homöopathischen Gruppe 10,1 mm ± 5,3 mm und in der Placebo-Gruppe 16,1 mm ± 9,1 mm, was statistisch nicht signifikant war ($P = 0,12$ bzw. $P = 0,11$). Es wurde ein signifikanter Unterschied im VAS-Score zwischen den Gruppen ($P = 0,039$) für Schmerzen festgestellt, und ein positiver Trend für Homöopathie wurde für Dysurie festgestellt. Ein verifiziertes Symptomsyndrom von Lycopodium wurde beobachtet.

Schlussfolgerung: Zukünftige Studien können mit pragmatischem Studiendesign und individualisierter Homöopathie durchgeführt werden, um die Wirksamkeit der homöopathischen Behandlung zu bewerten.

以石松治療尿石症：随机双盲安慰剂对照试验

背景：尿石症是世界上最常見的泌尿道疾病。常規治療包括各種合成和天然藥物和／或手術。 順勢療法文獻顯示順勢療法藥物對於排出和溶解結石有幫助。

目的：評價石松治療尿石症的療效，並查證其症狀；從而獲得順勢療法藥物治療急性腎絞痛的有效性。

方法：進行了一項多中心、隨機、雙盲安慰劑對照試驗。根據納入和排除標準對患者進行篩選，並且挑選出在使用療劑彙集分析法後指引出石松的患者。在急性腎絞痛期間，儘管進行了分組，患者要不使用指引出來的順勢療法藥物，就是使用常規藥物；使用視覺模擬量表（VAS）評估疼痛和排尿困難。

結果：在試驗期間排出結石的病例數目之間，各組之間並無統計學差異（$P = 0.31$）。 順勢療法組別排出的單一顆腎石平均大小為9.4mm ± 4.9mm，安慰劑組別為13.9mm ± 2.2mm；順勢療法組別多發性結石為10.1mm ± 5.3mm，安慰劑組別為16.1mm±9.1mm，無統計學差異（$P = 0.12$和$P = 0.11$）。兩組間疼痛的VAS評分有顯著差異（$P=0.039$），同時在順勢療法組別中伴有排尿困難的結果都有呈陽性趨勢。我們觀察到一種已證實的石松症狀綜合症。

結論：未來的研究可以通過實用性研究設計和個人化順勢療法進行，以評估順勢療法的有效性。