Effect of Alkalized Urine on Renal Calculi in Patients With Gout: a Protocol for a Randomized Controlled Trial

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Abstract

Background: The prevalence of renal calculi in patients with gout is high. Alkalized urine has been recommended by the 2020 European Association of Urology (EAU) guidelines to promote calculus dissolution. However, randomized controlled trials are lacking. Hence, it wasn't recommended by the 2020 American College of Rheumatology (ACR) guidelines.

Objective: The present study aimed to determine the effect of sodium bicarbonate-alkalized urine on renal calculus in patients with gout.

Methods: In this randomized, placebo-controlled, double-blinded trial, patients with gout combined with renal calculi are randomized (1:1) to the placebo and sodium bicarbonate groups. All patients were administered febuxostat (40 mg/day) and concomitant anti-inflammatory prophylaxis therapy. The 1–12-week group is double-blinded, and the 13–24-week group is open-labeled. The primary outcome is the rate of patients whose renal calculus volume is reduced after 12 weeks. The secondary outcomes included the volume changes of renal calculi, uric acid changes, the rate of patients with serum uric acid (sUA) levels < 360 μmol/L, the changes in estimated glomerular filtration rate (eGFR), the pH value of urine, and the adverse effects after 12 and 24 weeks.

Discussion: This trial would evaluate the efficacy and safety of sodium bicarbonate-alkalized urine on renal calculi in patients with gout.

Trial registration: ChiCTR, ChiCTR2100045183, Registered 7 April 2021
http://www.chictr.org.cn/showproj.aspx?proj=124742

Background

Gout is caused by the disorder of purine metabolism, increase in uric acid production, and/or the decrease in uric acid excretion, which leads to elevated sUA levels, forming monosodium urate (MSU) crystals and deposition in joints, surrounding the tissues and kidneys. The pooled prevalence of gout was 1.1% in China\textsuperscript{[1]}.

Nephrolithiasis is common in patients with gout. A meta-analysis showed that 24% of patients with gout are suffering from nephrolithiasis. The odds ratio (OR) of gout as a risk factor for nephrolithiasis is 2.41\textsuperscript{[2]}, and the hazard ratio (HR) of renal calculus as a risk factor for the development of end-stage renal disease (ESRD) is 2.34–6.18\textsuperscript{[3]}. More than half of the patients with nephrolithiasis are bilateral and multiple calculi carriers\textsuperscript{[4]}. The formation of renal calculi in patients with gout is mainly related to uric acid. A previous study analyzed uric acid composition in patients with gout by DECT and found that the proportion of pure and mixed uric acid renal calculus was 77.8\%\textsuperscript{[5]}. The ionized forms of uric acid readily form salts, namely monosodium urate, disodium urate, or potassium urate. In the extracellular fluid, sodium is the dominant cation. Supposedly, 98% of uric acid forms monosodium urate at pH = 7.4, and
the saturation of monosodium urate in human plasma is about 7 mg/dL. As urine acidifies along the renal tubules, a portion of urate is converted to uric acid. The solubility of uric acid in an aqueous solution is less than that of urate, but the saturation increases significantly with the increase in the pH value of urine. When pH 5, urinary uric acid saturation is 15 mg/dL, while the is 158–200 mg/dL at pH7, and the solubility of uric acid is increased by 20-fold\[5\]. Long-term high uric acid levels in patients with gout elevate the urinary uric acid concentration and form crystals after exceeding the solubility, which gradually enlarge and form calculus\[6\]. Previous studies have shown that the course of gout and low pH value of urine\[5\] are the primary hazard factors of renal calculus.

Another study suggested that the pH value of urine is increased from 5.5–6.0 by administering sodium bicarbonate (1 g tid) for 3 months in patients with gout\[7\]. Although several Associations of Urology recommended urine alkalization to promote calculi dissolution in nephrolithiasis\[8–11\], advanced evidence is lacking. Since alkalized urine may increase the risk of hypertension, water-sodium retention, and heart failure, the 2020 American College of Rheumatology (ACR) guidelines indicated that initiated urine alkalization is not recommended even in cases that stimulate excretion of uric acid. According to the composition, renal calculus is mainly divided into calcified calculi, urate calculi, cystine calculi, and combinations. Typically, nephrolithiasis is assessed by ultrasonography, plain film radiography, tomography, or excretory urography with an intravenous contrast agent\[12\]. However, none of these methods could identify calculi before treatment. dual-energy computed tomography (DECT) is a novel non-invasive technique that fundamentally distinguishes the composition of urate calculi. This method has been previously validated in the in vitro and in vivo studies\[12–15\]. Moreover, it can also calculate the volume of renal calculi. The study aimed to determine the effect of sodium bicarbonate-alkalized urine on renal calculus in patients with gout.

**Methods**

**Study design**

The study will be completed at Shenzhen Traditional Chinese Medicine Hospital and People’s Hospital of Longhua District Shenzhen, as a two-center, blinding, randomized, and placebo-controlled trial with two arms over 12 weeks. A total of 98 patients with gout combined with renal calculi who meet the study criteria are randomized (1:1) to the placebo and sodium bicarbonate groups. The intervention would be performed for 12 weeks with a follow-up of 24 weeks. The 1–12-week group is double-blinded, and the 13–24-week group is open-labeled. Informed written consent was obtained prior to the commencement of this study. All enrolled subjects would be fully informed about the purpose, process, and possible risks of the study (registration number: ChiCTR2100045183).

**Participants**

*Inclusion criteria*
Participants who met the following criteria would be included:

(1) Male and female patients 18–80-years-old;

(2) Fulfill the European League Against Rheumatism/American College of Rheumatology criteria for acute arthritis of gout in 2015;

(3) B-ultrasound suggested renal calculi;

(4) Male has no fertility requirement in recent 6 months;

(5) Female who underwent sterilization operation or menopause for 2 years;

(6) Informed written consent was obtained.

Exclusion criteria:

Potential subjects who met the inclusion criteria would be excluded if they meet any of the following:

(1) Allopurinol, probenecid, benzbromarone, and febuxostat tablets were used for urate-lowering treatment (ULT) in the first 4 weeks of enrolment;

(2) Renal calculus >15 mm, obstruction (hydronephrosis), pain, and urinary tract infection requiring lithotripsy;¹⁰

(3) Patients with secondary hyperuricemia caused by kidney disease, hematopathy or some medications, tumor chemoradiotherapy, and organ transplantation;

(4) Patients with a history of cardicocerebrovascular diseases, such as stroke, TIA, MI, HF (NYHA II-IV), coronary artery surgery (for example, angioplasty, stent implantation, and bypass grafting);

(5) Patients have histories of peptic ulcer and gastrointestinal bleeding;

(6) Patients with active stage of liver disease, abnormal liver function or transaminase is 1.2-fold higher than the upper limit of normality;

(7) Patients with abnormal renal function and eGFR <60 mL/min.1.73 m²;

(8) Patients also having malignant tumor or psychosis;

(9) Patients with allergic or intolerant to febuxostat;

(10) Other (non-gout) chronic arthritis, acute inflammatory arthritis, and autoimmune diseases associated with arthritis;
(11) Those administering or need azathioprine, mercaptopurine, theophylline, and cytotoxic chemotherapeutic drugs;

(12) Patients with a history of alcohol or drug dependence or need long-term daily painkillers for any reason;

(13) Patients who have been involved in other clinical investigations in the first 3 months of enrolment;

(14) Other situations that the investigators deem unsuitable for the patient to enter the clinical trial.

Rejection criteria

(1) The combination of drugs in violation of the protocol or failure to use drugs in accordance with the provision that in turn affects the outcomes;

(2) Incomplete data affect the efficacy and the judgment of safety.

Shedding criteria

(1) Serious adverse reactions related to the study drug;

(2) In this study, major mistakes were detected in the clinical research protocol, which made it difficult to evaluate the efficacy of the drug. Also, a significant deviation was observed in the implementation of a well-designed protocol.

Subject termination criteria

(1) Subject terminates spontaneously (for example, withdrawal of the informed consent);

(2) Subject is pregnant (must drop out of the study);

(3) Subject uses a combination of drugs within a non-prescribed range, which affects the judgment of efficacy and safety.

(4) Indexes of liver function: transaminase $\geq 3$ times the upper limit of normality for $>1$ week;

(5) Worse or adverse events in the subject that led the investigator to decide that the subject has to quit early;

(6) Other investigators consider that the subject is not suitable to continue and need to quit;

(7) Compliance of the subject to the research protocol is poor, and the quantity and duration of medication are not between 80% and 120%.

Participant recruitment
The controlled, randomized, assessor, and patient blinded trial will be conducted at Shenzhen Traditional Chinese Medicine Hospital and People’s Hospital of Longhua District Shenzhen, wherein medical service would be provided for patients with gout combined with renal calculi. The subjects in this study will be recruited from outpatient and inpatient by placing advertisements on social media platforms of the hospital departments and distributing posters in public areas of the hospital with details of the study and contact information.

Subjects interested would be welcome to contact the investigators by phone or on-site for initial screening. Potential participants would be enrolled, and an appointment made with a designated physician to examine the inclusion and exclusion criterion. Patients who met the criteria will be invited to participate in the study, and details of the clinical randomized controlled trial will be provided. All subjects will be required to sign an informed written consent and provide complete information. The subjects will be randomized (1:1) to the placebo and sodium bicarbonate groups. None of the patients would know about their assigned group in order to keep the blind in the trial. Then, the baseline characteristics would be assessed and a database record obtained by the same physician. All subjects will be treated for 24 weeks and followed up on 4, 12 and 24 weeks; the data will be evaluated. In addition, all the subjects will be given a schedule of intervention dates and follow-up appointments. These evaluations would be performing by an assistant who is involved neither in the randomization nor in the treatment.

**Randomization and blinding**

A total of 98 eligible subjects were randomly assigned to two parallel groups. Statisticians adopted the PROC PLAN process of SAS 9.4 statistical software to generate a random list by blocked randomization of variable block lengths. Then, the clinical trial managers divided them into two groups according to the random list. All involvers and investigators are blinded to the assignment of the subjects. The placebo is similar to sodium bicarbonate in size, weight, shape, and color. Doctors, subjects, and data analysts are unclear about the type of drug. The randomized assignment sequence is placed in a sealed opaque envelope whereas the blind codes are kept at the department of research management and can be reproduced when needed.

**Intervention**

1. Sodium bicarbonate group: sodium bicarbonate (1 g tid).
2. Placebo group: sodium bicarbonate placebo (1 g tid).
3. Both groups are administered febuxostat (40 mg/day) for ULT.
4. Drugs to prevent gout flares: prednisone acetate (5 mg Qd), celecoxib, or colchicine (12 weeks).
5. Trial period: The 1–12-week group is double-blinded, and the 13–24-week group is open-labeled.
During this trial, all subjects received general treatment, including strict diet: intake of low-calorie diet to maintain ideal body weight. Avoid food with high purine content, such as animal offal, thick gravy soup, sardines, and clams, oysters. The moderate consumption of fish, shrimp, meat, and pea with a moderate amount of purine. The daily diet consists of low purine content of cereal products, fruits, vegetables, milk, dairy products, and eggs. Also, drinking >2000 mL of water every day and give up all kinds of alcohol strictly. Avoid inducements: smoking, overeating, cold, dampness, overfatigue, and stress. In addition, it is necessary to slip into comfortable shoes, prevent damage of joint, and only sparingly use drugs that seriously affect uric acid excretion (such as some diuretics). Concomitant disease control: simultaneously treat associated hyperlipidemia, diabetes, hypertension, coronary heart disease, and cerebrovascular disease.

**Research procedures**

- **Screening:**

  In line with ACR and European League Against Rheumatism, EULAR) criteria and the score system for acute arthritis of gout in 2015; B ultrasonography suggested renal calculi. The patients were 18–80-years-old.

- **Enrolment:**

  Each subject will be interviewed by investigators prior to the start of the treatment, and the data would be input into the database along with initial data at the study baseline. The subjects will be divided into test and control groups according to the treatment, and both groups will be treated for 6 months. Renal calculus volume changes before and after treatment will be observed, respectively.

- **Treatment scheme:**

  Test group: sodium bicarbonate 1 g tid combined with febuxostat 40 mg/d and prednisone acetate 5 mg Qd for 12 weeks.

  Control group: placebo 1 g tid combine with febuxostat 40 mg/d and prednisone acetate 5 mg Qd for 12 weeks.

- **Laboratory indicators:**

  Blood routine, urine routine, liver and renal function, Erythrocyte sedimentation rate (ESR), C reactive protein (CRP), and renal DECT.

- **Follow-up:**

  Follow-up will be conducted at baseline, 12 weeks±5 days, and 24 weeks±5 days.

- **Specimen collection:**
The demographic data of the subjects were collected with respect to age, gender, course of the disease, and history. The subjects were followed up three times (baseline, 12 weeks, and 24 weeks after the treatment) to detect blood routine, liver, kidney function, and ESR. Before curing, cured after 24 weeks, test and evaluate predictors of related systems damage. Biological specimens will be destroyed after testing.

**Outcome measurements**

**Primary outcomes**

The rate of patients whose renal calculus volume is reduced after 12 weeks.

**Secondary outcomes**

The volume changes of renal calculi, uric acid changes, the rate of patients whose sUA levels are \(<360 \mu\text{mol/L}\), the changes in eGFR, the pH value of urine, and adverse effects after 12 and 24 weeks.

Adverse events will be monitored during the 24 weeks of treatment, including the incidence of hypertension before and after treatment, the incidence of post-treatment edema, and the rate of acute gout attack within 12 weeks. Any adverse reactions that occur during the study will be recorded in the “Adverse Reaction Table,” and the patients will be followed up until symptoms disappear or indicators return to normal. In the event of serious adverse events, necessary measures will be taken immediately to ensure the safety of the subjects. In addition to evaluating the primary and secondary outcomes, safety assessment will be conducted at baseline and week 24 with respect to blood pressure, respiration, heart rate, blood routine, urine routine, liver and renal function, ESR, CRP, and renal DECT. (Figure 1 and Figure 2)

**Sample size**

This is a differential test. The primary outcome is the rate of patients whose renal calculus volume is reduced after 3 months. According to the hypothesis, the test level was a two-sided P-value of 0.05 and power of 80%, while the ratio of the sodium bicarbonate to the placebo group was 1:1. The parameters of preliminary studies demonstrated that the reduction rate of renal calculus volume in the test group was 89.74% in 3 months, while that in the control group was 64.10%. The estimated sample size for each group was 42 and was 84 for the two groups, respectively. In this study, the shedding rate did not exceed 15%, and the sample size for each group was determined to be 49.

**Trial monitoring**

The Steering Committee consists of three members with two senior rheumatologists and a statistician to supervise the trial and ensure the safety and quality of data. The committee is independent of the research team and has no conflict of interest with the investigators. They will provide regular supervision, hold monthly meetings, and organize a field trip at least once to ensure the trial is carried out smoothly and ethically. Also, a supervisor would ensure the authenticity and integrity of the data. During the visit,
they will interview the investigators, check the original research documents and the registration of subjects, and confirm whether the clinical center complies with the research protocol. Any non-compliance with the agreement will be fully recorded using a violation report form. Furthermore, they will also identify the problems in the trial and put forward suggestions on the modification of the protocol. If any decision to amend the protocol has to be made, the approval will be applied to the Institutional Medical Ethics Committee in writing, and the investigator will be notified in writing after approval. The protocol will be updated immediately in the system.

Data management

The data of this clinical trial is managed by Zhiying Zhan (Public Health school of Fujian Medical University), which ensures the authenticity, integrity, and privacy of clinical test data during the research process. The clinical trial database is structured by the appointed data manager who is responsible for the regular database management and maintenance. All of the data will be imported into the clinical trial database by two research assistants. Any missing or incorrect data will be detected by software system. In such case, the original CRFS will be checked to correct or complete every piece of data.

Statistical analysis

Multiple imputation was used to manage missing values. Study populations included the intent to treat (ITT) analysis set, defined as all randomized patients; the per-protocol (PP) analysis set, defined as all patients in the ITT population without any major protocol deviations. The primary outcome will be compared between the groups using Pearson’s chi-square test. T-test, corrected T-test (equal variance not assumed), and analysis of variance (ANOVA) for repeated measurements will be used for measurement data, and the grade data will be assessed by Wilcoxon two-sample test. The hybrid control will use multivariate logistic regression, estimating the odds ratio (OR) and 95% confidence interval (CI). Clinically significant variables in the univariate analysis will be included in the multivariate model. The goodness of fit will be evaluated by Hosmer–Lemeshow test. Statistical analysis was carried out using SPSS (version 26). A two-tailed significance level of 0.05 was used for all tests. P<0.05 indicated statistical significance.

Publication policy

All presentations should protect the integrity of the primary research objective. Any data that compromises the blinding would not be released before the outcomes. The Steering Committee will discuss the recommendations on the timing of these final data that may be presented at the meetings. The primary outcomes will be published in abstract books and as articles.

Ethical considerations

The Institutional Medical Ethics Committee of Shenzhen Traditional Chinese Medicine Hospital (Registration number: K2021-010) and People’s Hospital of Longhua District Shenzhen have approved the protocol and informed written consent. Investigators are responsible for explaining the benefits and risks involved in the trial to each patient or his/her legal representative. The written consent was obtained
before enrollment. The subjects in the trial had participated voluntarily and had the right to refuse to enroll or withdraw at any stage without discrimination or retaliation, and their treatment and medical right would not be affected.

The confidential measures were as follows. The outcomes of this project might be published in medical journals. The information of the subjects would be represented by a unique number, and the coded information would be stored in Public Health school of Fujian Medical University. The information of subjects was maintained confidential as required by law. However, records of subjects may be reviewed to ensure that the study complies with applicable laws and regulations.

**Discussion**

In patients with gout, vascular injury caused by hyperuricemia and the deposition of urate crystals in the medulla is a major cause of substantial kidney damage, increasing the risk of chronic kidney disease and thus exerting a significant impact on the living quality of patients. Xanthine oxidase inhibitors alone are not as effective in preventing renal calculi as drugs that alkalize urine. The common drugs are sodium bicarbonate and potassium sodium hydrogen citrate. However, both give rise to adverse reactions, resulting in poor patient compliance [16]. Furthermore, recommendations by the 2020 ACR and EAU guidelines for the therapy of renal calculi in patients with gout by alkalizing urine are controversial [10,11]. Due to lack of strong evidence, we designed a randomized controlled trial to analyze the effect of urine on renal calculi in patients with gout by evaluating whether the renal calculus volume is reduced after 12 weeks. In order to provide guidelines using an accurate medical method, such as urine alkalization for patients, thereby reducing the incidence of gout flares.

Nevertheless, the present study has some limitations. First, the universality of the sample population and the research centers involved in the trial is limited. In order to complete this clinical trial successfully, the selected participants should be local residents from Shenzhen, which would ensure their participation throughout the treatment. Patients with gout combined with renal calculi under investigation might not have urate calculi, as identified by DECT. In addition, the EAU guidelines recommend administration of allopurinol during ULT, requiring sUA levels of each case to be appropriate to the standard (> 4.0 mmol/d and/or > 380 µmol/L) [11]. Previous studies have shown that gout patients have a high rate of sUA less than 360 µmol/L who treated with febuxostat (40 mg/d) in China[17]. Taken together, this clinical trial aimed to explore if urine alkalization is suitable for patients with gout combined with renal calculi and whether the associated adverse effects could be avoided. Finally, we hoped that clinicians and patients with gout focus on the therapeutic pathway of renal calculi by alkalizing the urine.

**Trial status**

The revised version of V20210423 on April 23, 2021 has been approved by the Institutional Medical Ethics Committee of Shenzhen Traditional Chinese Medicine Hospital and People’s Hospital of Longhua District Shenzhen. The recruitment will begin on July 1, 2021, and this study will complete on June 30, 2023.
Declarations

Acknowledgment

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Authors’ contributions

EJ, JZ and FL designed the randomized placebo-controlled trial. EJ, HG and HZ drafted the manuscript. YW, LZ, SL and JZ conducted the research. EJ were responsible for the statistical analyses. All authors participated in the manuscript revision.

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Conflict of Interest

The authors declare they have no conflicts of interest.

DATA SHARING STATEMENT

Data are available upon reasonable request. For inquiries about data sharing, please send request at sailing1980@126.com.

Ethics approval and consent to participate

The study is approved by the Institutional Medical Ethics Committee of Shenzhen Traditional Chinese Medicine Hospital (approval number: K2021-010). All the subjects are required to sign consent forms to confirm their participation.

Consent for publication

Not applicable

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Figures

The effect of alkalized urine on renal calculi in patients with gout: A double-blind randomized controlled trial

- Research background
- Screening patients with gout combined with renal calculi > 98
- Sodium Bicarbonate N=49
- Placebo N=49
- Flow-up
  - baseline
  - 12 weeks ± 5 days
  - 24 weeks ± 5 days
- Research analysis
- Evidence that alkalized urine promotes calculi dissolution
- Risk assessment of alkalized urine

Conclusion and prospect

Figure 1
### Trial flow and study design.

| STUDY PERIOD          | Enrolment | Allocation | Post-allocation |
|-----------------------|-----------|------------|-----------------|
| TIMEPOINT (week)      | -1        | 0          | 12              |
|                       |           | 24         |                 |
| **ENROLMENT**         |           |            |                 |
| Eligibility screen    | [x]       |            |                 |
| Informed consent      |           | X          |                 |
| Demographic           |           |            |                 |
| characteristics       | X         |            |                 |
| Medical history       |           | X          |                 |
| Laboratory tests      |           | X          |                 |
| Randomization         |           | X          |                 |
| Allocation            | [x]       |            |                 |
| **INTERVENTIONS**     |           |            |                 |
| Sodium bicarbonate    |           |            |                 |
| Placebo               |           |            |                 |
| **ASSESSMENTS**       |           |            |                 |
| Renal [DECT]          | X         | X          | X               |
| sUA                   | X         | X          | X               |
| eGFR                  | X         | X          | X               |
| pH value of urine     | X         | X          | X               |
| Blood pressure        | X         | X          | X               |
| Respiration           | X         | X          | X               |
| Heart rate            | X         | X          | X               |
| Blood routine         | X         | X          | X               |
| Urine routine         | X         | X          | X               |
| Liver function        | X         | X          | X               |
| ESR                   | X         | X          | X               |
| CRP                   | X         | X          | X               |
| Adverse Event         | X         | X          | X               |

**Figure 2**

SPIRIT figure of enrolment, interventions, and assessments. DECT dual-energy computed tomography, sUA serum uric acid, eGFR estimated glomerular filtration rate, ESR Erythrocyte sedimentation rate, CRP C reactive protein.
Supplementary Files

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- SPIRITchecklist.docx