

Effects of Keluoxin Capsule Combined with Losartan Potassium on Diabetic Kidney Disease with Qi and Yin Deficiency and Blood Stasis Syndrome: Study Protocol for a Randomized Double-Blind Placebo-Controlled Multicenter Clinical Trial

Rui Wu

Guang'anmen Hospital, China Academy of Chinese Medical Sciences

Junping Wei (✉ weijunping@126.com)

Fan Wei

China Academy of Chinese Medical Sciences Guanganmen Hospital

Lianlian Qu

Penglai Traditional Chinese Medicine Hospital

Litao Bai

Chongqing Medical University Second Affiliated Hospital

Jun Li

China Academy of Chinese Medical Sciences Guanganmen Hospital

Fei Li

China Academy of Chinese Medical Sciences Guanganmen Hospital

Weitian Yan

China Academy of Chinese Medical Sciences Guanganmen Hospital

QiuHong Wang

China Academy of Chinese Medical Sciences Guanganmen Hospital

Study protocol

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Abstract

Background: Diabetic kidney disease (DKD) is one of the most important microvascular complications of diabetes, and its prevalence has increased dramatically in the past few decades. DKD is responsible for considerable morbidity and mortality of patients with diabetes. Keluoxin capsule (KLX) is a Chinese patent medicine that has been used in the clinic to control DKD for years. Thus, we aim to evaluate whether losartan potassium combined with KLX is more effective than losartan potassium in DKD treatment and to provide validated evidence for the application of KLX in the treatment of DKD.

Methods: We will conduct a randomized double-blind placebo-controlled multicenter clinical trial. A total of 252 participants diagnosed with DKD recruited from 18 institutions will be randomly allocated to either a KLX treatment group ($n=126$) or a placebo control group ($n=126$). The participants will be administered KLX or placebo in addition to losartan potassium for 24 weeks. The primary outcome measure will be the decline in the estimated glomerular filtration rate (eGFR; ml/min/1.73 m²/year) from baseline within 24 weeks, and the secondary outcomes will be the incidence of serum creatinine doubling, the incidence of end-stage renal disease (ESRD), the proportion of subjects with a progressive decline in eGFR >30%, the percent change in 24 h urinary total protein (UTP), the change in the urinary albumin/creatinine ratio (UACR), and the traditional Chinese medicine (TCM) syndrome scale scores.

Discussion: This study will be the first randomized clinical trial to evaluate the efficacy and safety of KLX versus placebo for the treatment of patients with DKD. The outcome of this trial will provide a basis for prescribing KLX to patients with DKD.

Trial registration: The trial was registered at Chinese Clinical Trial Registry (www.chictr.org.cn) under approval number ChiCTR1900021113 (approval date: 2019/01/29).

Background

Diabetic kidney disease (DKD), a chronic progressive disorder that is characterized by proteinuria and an irreversible decline in renal function, ultimately leads to end-stage renal disease (ESRD) in approximately 50% of patients in developed countries [1, 2]. DKD is one of the most important microvascular complications of diabetes, and its prevalence has increased dramatically worldwide in the past few decades [3, 4]. It has been reported that DKD accounts for approximately 20% of new dialysis prescriptions [5], and the high medical cost of renal dialysis treatment has created an urgent need for additional therapeutic strategies for DKD [6]. Comprehensive measures such as hypoglycemic and antihypertensive treatments have demonstrated beneficial effects in preventing the development of DKD, especially when used at the stage of microalbuminuria, and angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor II blockers (ARBs) reduce the risk of progression of DKD [7–9]. However, combinations of traditional Chinese medicine (TCM) and Western medicine have advantages over Western medicine in delaying the progress of CKD and improving quality of life.

Keluoxin capsule (KLX) is a Chinese patent drug developed by the Chengdu Kanghong Pharmaceutical Co., Ltd. and Guang'anmen Hospital of the China Academy of Chinese Medical Sciences. It consists of *Astragalus membranaceus*, *Ligustrum lucidum*, leech, rhubarb, Radix Pseudostellariae and the fruit of the Chinese wolfberry. It is used for DKD in patients with syndromes of qi and yin deficiency and blood stasis because it nourishes qi and yin, promotes blood circulation and removes blood stasis. KLX was once named Tangshenping or Tangweikang. Research on KLX for DKD is included in the national Ninth Five-Year Plan project.

KLX was placed on the market in 2009 and is considered a B category drug by Chinese medical insurance. Previous studies have shown that KLX can regulate glucose and lipid metabolism, improve renal hemodynamic parameters and protect against pathological damage in diabetic rats [10]. It can also reduce high glomerular perfusion and filtration rates and thus delay the processes of glomerular fibrosis and hardening in diabetic nephropathy rat models [11]. In addition, KLX was approved for clinical trials by the State Food and Drug Administration in 2003. The results of the trials showed that KLX is effective in controlling 24 h urinary total protein (UTP) levels, urinary albumin (ALB)/creatinine ratios (UACRs) and TCM syndrome scale scores [12, 13]. Moreover, both acute toxicity tests and long-term toxicity tests have verified the safety KLX in the treatment of DKD.

However, there is a lack of validated evidence regarding the effectiveness of KLX on DKD. Therefore, in the proposed study, we will conduct a randomized double-blind placebo-controlled multicenter clinical trial to evaluate whether KLX combined with losartan potassium tablets is more effective in delaying the progression of DKD than losartan potassium tablets based on the pathophysiological mechanism of the development of DKD.

Methods/design

Study objectives

The objective of this trial is to evaluate whether the effect of losartan potassium combined with KLX is superior to that of losartan potassium in DKD treatment and to obtain validated evidence for the application of KLX in the treatment of DKD.

Study design

This will be a double-blind randomized controlled trial to investigate the efficacy of KLX combined with losartan potassium compared with a placebo. The study will be conducted in eighteen centers in China: Guang'anmen Hospital of the China Academy of Chinese Medical Sciences, Dongzhimen Hospital of Beijing University of Chinese Medicine, the First Affiliated Hospital of Chengdu Medical College, Mianyang Central Hospital, the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine, Dazhou Central Hospital, Dezhou People's Hospital, Linfen Central Hospital, the Affiliated Hospital of Liaoning University of Traditional Chinese Medicine, the First People's Hospital of Luoyang, Shenzhen Hospital of Southern Medical University, Shanghai Shuguang Hospital, Yueyang Hospital of Integrated Traditional

Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, the Second Affiliated Hospital of Wannan Medical College, Nanyang City Central Hospital, the First Affiliated Hospital of Henan University of Chinese Medicine, Xinxiang Central Hospital, and Heze Municipal Hospital. Patients with DKD who want to participate in the study will undergo a standardized baseline evaluation before treatment including detailed history evaluation, physical examination, and laboratory testing. The enrolled participants will be randomly allocated to the KLX treatment and placebo control groups. The participants will be administered KLX or placebo in addition to losartan potassium for 24 weeks. Data will be collected during three visits to assess the efficacy of KLX and will be recorded on case report forms (CRFs). A flowchart of the study design is shown in Fig. 1, and the time points of assessment are shown in Table 1. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [14] were followed during the development of the protocol of this study.

Table 1
Schedule of
enrollment,
intervention,
and
assessment

Study settings and recruitment

Assuming a 20% dropout rate, a total of 252 patients will be recruited from the eighteen centers mentioned above using posters, the hospitals' websites, and networks from December 2019 to December 2020. Research assistants will manage the recruitment, and endocrinologists will diagnose the participants.

Participants

Subjects will be deemed eligible participants if they meet all of the listed inclusion criteria and none of the listed exclusion criteria.

- Inclusion criteria.
 1. Diagnoses of type 2 diabetes and DKD;
 2. Diagnoses of TCM syndromes of qi and yin deficiency and blood stasis;
 3. A UACR $\geq 30 \text{ mg/g}$;
 4. An estimated glomerular filtration rate (eGFR, according the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation) $\geq 30 \text{ ml/min}/1.73 \text{ m}^2$ and $\leq 59 \text{ ml/min}/1.73 \text{ m}^2$;
 5. A fasting blood glucose level $< 13.9 \text{ mmol/L}$ and/or a 2 h postprandial blood glucose level $< 16.6 \text{ mmol/L}$;
 6. A glycated hemoglobin (hemoglobin A1c, HbA1c) percentage $\leq 10\%$;
 7. An age between 35 and 75 years, male or female;
 8. Voluntary participation in this clinical study and provision of written informed consent.
- Exclusion criteria.

1. A diagnosis of type 1 diabetes;
2. A lack of diagnosed diabetic retinopathy;
3. A history of simple renal hematuria or proteinuria with hematuria; sudden onset of edema and mass proteinuria without abnormal renal function; significant renal tubular dysfunction; coexisting renal tubular abnormalities; primary glomerulonephritis or secondary nephritis except DKD; or acute or chronic infection of the urinary system;
4. A hemoglobin (HGB) concentration < 90 g/L;
5. An ALB concentration < 30 g/L;
6. A diagnosis of renal artery stenosis;
7. A serum potassium concentration > 5.5 mmol/L;
8. A serum creatinine (Scr) concentration \geq 3 mg/dL (256 μ mol/L);
9. A history of severe cardiovascular or cerebrovascular disease within three months before screening;
10. Severe systemic primary disease or dysfunction;
11. Severe liver dysfunction or ALT or AST levels higher than 2.5 times the normal range;
12. Hypertension treated with more than 3 kinds of antihypertensive drugs, blood pressure that is poorly controlled after administration of drugs with a systolic blood pressure (SBP) \geq 140 mmHg or a diastolic blood pressure (DBP) \geq 90 mmHg, or hypotension with an SBP \leq 90 mmHg or a DBP \leq 60 mmHg (resting position);
13. Chronic (for more than 3 weeks) or recurrent diarrhea (where diarrhea is defined as elimination of increased volumes of thin fecal matter with increased frequency (> 3 times/day));
14. A history of active bleeding in the 3 months before screening;
15. Coagulation disorders;
16. Drug allergies or allergies to KLX or the active ingredient in losartan potassium;
17. A history of alcohol or drug abuse or psychiatric disorders;
18. Pregnancy, lactation or plans to become pregnant during the trial;
19. A history of enrollment in other clinical studies in the past 3 months;
20. Other circumstances under which the investigators considered it inappropriate to participate in this clinical study.

Randomization, allocation concealment, and blinding

The participants will be randomly assigned to either the KLX group or placebo group in a 1:1 ratio. Randomization will be performed using Statistics Analysis System (SAS) software by an independent statistical agency. The Institute of Data Management Center of Guang'anmen Hospital will be responsible for drug blinding and randomization concealment. The drug administrator will enroll patients at the 18 participating medical centers sequentially on the basis of screening order. Both the participants and the investigators will be kept blinded to the allocations until the trial is completed. In case of a severe adverse event, an administrator at the Data Management Center of Guang'anmen Hospital will unblind the patient information as an emergency measure and provide relevant treatment.

Intervention

All investigators will be trained before the start of the study according to an investigators' brochure. The enrolled patients with DKD will be asked to take losartan potassium tablets (50 mg per day) as the basic treatment and will also be administered KLX or placebo. The subjects in the treatment group will take four capsules of KLX orally thrice a day for 24 weeks. The participants in the placebo control group will take the same amount of placebo for 24 weeks. Data from all the participants will be collected in four periods: on day 0 (V2), at 4 weeks \pm 3 days (V3), at 12 weeks \pm 5 days (V4), and at 24 weeks \pm 5 days (V5).

The placebo is identical in appearance and properties to KLX capsule without any active ingredient. Both KLX and the placebo will be manufactured by Chengdu Kanghong Pharmaceutical Co., Ltd., at a dose of 500 mg. The placebo, whose appearance and properties will be identical to those of KLX, will contain no active ingredients. The placebo will be verified by the quality control department and will meet the standards of placebo preparation. The interventions should stop for a given participant if the creatinine doubles or ESRD is detected. The participants will be asked to refrain from taking any other treatment for diabetic nephropathy, including ACEI or ARB drugs other than losartan potassium tablets, calcium hydroxybenzenesulfonate, etc. as well as Chinese medicine that affect evaluation of qi and yin deficiency and blood stasis syndrome during the trial.

Outcome measures

- Primary outcomes.

The primary endpoint is the decline in the eGFR (ml/min/1.73 m²/year).

- Secondary outcomes.

The secondary outcomes will include the incidence of Scr doubling, the incidence of ESRD, the proportion of subjects with a progressive decline in eGFR of > 30% from baseline within 24 weeks, the percent change in 24 h UTP, the change in UACR and the TCM syndrome scale scores.

- Safety assessments.

To assess the safety of KLX treatment in patients with DKD, vital signs and some laboratory parameters will be measured and electrocardiography will be performed during the intervention period of the trial. In detail, the vital signs will include body temperature, blood pressure, respiratory rate and pulse rate. The biological indicators we will monitor will include routine blood indices (red blood cell count (RBCs), hemoglobin(HGB), white blood cell count (WBCs), and platelet count (PLTs)), routine urine and urine sediment parameters (assessed under microscopy), 24 h UTP levels, UACRs, liver function indices (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBIL), and γ -glutamyl transferase (GGT)), renal function indices (eGFR and Scr), serum electrolytes (K^+ , Na^+ , and Cl^-), blood lipid profile indices (total cholesterol (TC), triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C)), coagulatory function indices (prothrombin time (PT), activated partial thromboplastin time (APTT), and fibrinogen

(FIB)), HbA1c levels, and fasting blood glucose levels. Moreover, detailed information about any adverse events will be recorded, including the severity, rate of incidence, and correlation with the treatment.

Follow-up

All included participants will be re-evaluated at 6 and 12 months through phone calls or as outpatients.

Statistics

- Sample size.

This study will be a trial of a new therapeutic regimen of KLX treatment. The sample size was calculated using software PASS based on a similar study on a Chinese herbal medicinal supplement conducted previously [15]. Allowing for a 20% withdrawal rate, we plan to include 126 patients in this trial.

- Data analyses.

The independent researchers performing the biochemical tests, assessing the clinical outcomes, and analyzing the data will be kept blinded to the patients' identities and grouping. All data will be analyzed using Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS, Inc., Chicago, IL) software. Comparisons will be made using chi-square tests for count data. Statistical significance will be considered for a p value < 0.05.

- Data collection and management.

All researchers in this study will be qualified physicians and will receive training in standard operating procedures for trial execution, biological sample collection, and handling. Based on the initial observation records, all center investigators will complete the CRFs in an accurate and timely manner. The administrators of Guang'anmen Hospital will visit each center regularly to ensure the quality of data collection and to facilitate problem solving. All files will be properly classified and saved/archived under confidential conditions.

Discussion

DKD is the largest contributor to ESRD worldwide and is the leading cause of morbidity and mortality in patients with diabetes [16]. Methods to control DKD are urgently needed due to the increasingly high incidence of diabetes worldwide. Treatment of DKD mainly focuses on glycemic control, blood pressure reduction, and renin-angiotensin-aldosterone system (RAAS) blockade [17, 18]. TCM plays considerable roles in symptom and quality of life improvement for DKD patients in China. Therapies integrating Chinese and Western medicine have shown some benefits in delaying the progress of DKD and improving the quality of life of patients [19]. KLX, an empirical prescription for DKD, has been used in the clinic for years. The proposed trial aims to examine the efficacy and safety of KLX in comparison with placebo for the treatment of mild DKD. A prospective cohort design will be employed in the study, and 252 DKD patients will be treated as subjects.

Previous studies have shown that KLX can reduce the blood glucose levels and regulate the lipid metabolism of DKD patients [13]. It also relieves glomerular endothelial cell damage, protects renal function, improves hemodynamics and promotes renal microcirculation [20, 10]. However, there have been some limitations in previous clinical trials, such as lack of training for investigators, small sample sizes and short observation periods. To ensure the quality of the trial, some specific measures will be taken in the proposed study. First, patients will be enrolled from 18 study centers to minimize bias, and all subjects will be screened strictly. Second, the investigators will be trained and asked to carry out the trials according to the researcher's manual. Third, the inclusion criteria will include eGFR and TCM syndrome scale scores. Both subjective and objective indicators have been selected for comprehensive assessment of efficacy. Fourth, a placebo similar in appearance and taste to KLX will be used. In addition, although the pathogenesis of DKD remains unclear, most scholars believe that it is closely related to abnormal renal hemodynamics and disorders of RAAS [21]. Therefore, ACEIs and ARBs are commonly used to treat DKD because both ACEIs and ARBs can antagonize the activity of RAAS and reduce glomerular sclerosis and proteinuria [9]. Hence, as a control variable, losartan potassium will be given to both the treatment and placebo groups from the screening time point until the end of intervention. Fifth, a third-party randomization scheme will be applied for allocation concealment and double blinding.

This study will be the first randomized clinical trial to evaluate the efficacy and safety of KLX versus placebo for the treatment of patients with DKD. The outcome of this trial will provide a basis for prescribing KLX to patients with DKD.

Trial Status

The trial was carried out according to study protocol Version 2.0 on December 6th, 2019. Participant recruitment began in September 2019 and will finish in December 2020 as expected.

Abbreviations

DKD

diabetic kidney disease, KLX = Keluoxin capsule, TCM = traditional Chinese medicine, CRF = case report form, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, UTP = urinary total protein, UACR = urinary albumin/creatinine ratio, ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor II blocker, Scr = serum creatinine, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = γ -glutamyl transferase, ALP = alkaline phosphatase, TBIL = total bilirubin, TG = triglyceride, TC = total cholesterol, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, PT = prothrombin time, APTT = activated partial thromboplastin time, FIB = fibrinogen, HbA1c = hemoglobin A1c.

Declarations

Ethics approval and consent to participate

This study has been registered at Chinese Clinical Trial Registry under approval number ChiCTR1900021113 and was approved by the ethics committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences (Beijing, China; approval number: No.2018-158-KY-03). The informed consent will be obtained from each participant.

Consent for publication

Not Applicable.

Availability of data and material

The datasets of study will be available via the corresponding author on reasonable request, and the results will be published in peer-reviewed journals.

Competing interests

We have no conflicts of interest to disclose.

Funding

This trial will be supported financially by the Central Health Research Project (No. W2017BJ43) and the project leader is Prof. Junping Wei who is responsible for the trial design, the execution process and the manuscript reviewing.

Authors' contributions

Conceptualization: Rui Wu, Litao Bai and Junping Wei.

Data curation: Jun Li and Fei Li.

Formal analysis: Lianlian Qu and Litao Bai.

Methodology: Weitian Yan.

Project administration: Rui Wu and Fan Wei.

Supervision: Junping Wei.

Writing – original draft: Rui Wu and Fan Wei.

Writing – review & editing: Junping Wei, Lianlian Qu and QiuHong Wang.

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Table 1

Table 1 Schedule of enrollment, intervention, and assessment

	Study period							
	Enrollment	Allocation	Intervention			Follow-up		
Time point	-2 weeks	0 weeks	4 weeks	12 weeks	24 weeks	6 months	12 months	
Enrollment:								
Eligibility screening	x	x*						
Informed consent	x							
Unification of losartan potassium	x*							
Allocation	x [†]	x*						
Interventions:								
KLX								
Placebo								
Assessments:								
Results of pretreatment with losartan potassium		x*						
Medical history	x							
Physical examination	x	x*	x	x	x	x	x	
eGFR, Scr	x	x*	x	x	x	x	x	
Serum electrolytes	x	x*	x	x	x	x	x	
Routine blood and urine	x	x*	x	x	x	x	x	
24 h UTP	x	x*	x	x	x	x	x	
UACR	x	x*	x	x	x	x	x	
ALT, AST, ALP, TBIL, GGT	x			x	x	x	x	
TC, TGs, HDL-C, LDL-C	x			x	x	x	x	
PT, APTT, FIB	x		x	x	x	x	x	
Glycated hemoglobin	x			x	x	x	x	
Blood glucose	x	x*	x	x	x	x	x	
Electrocardiography	x				x		x	
Abdominal ultrasound	x							
TCM scores	x	x*	x	x	x	x	x	
Adverse events		x*	x	x	x	x	x	

Abbreviations: 24 h UTP, 24 h urinary total protein; UACR, urinary albumin/creatinine ratio; eGFR, estimated glomerular filtration rate; Scr, serum creatinine; PT, prothrombin time; APTT, activated partial thromboplastin time; FIB, fibrinogen; ESRD, end-stage renal disease; ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; TC, total cholesterol; TGs, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TCM = traditional Chinese medicine. x* only for subjects that undergo losartan potassium unification (50mg per day). x[†] only for subjects that take losartan potassium as 50mg per day before enrollment.

Figures

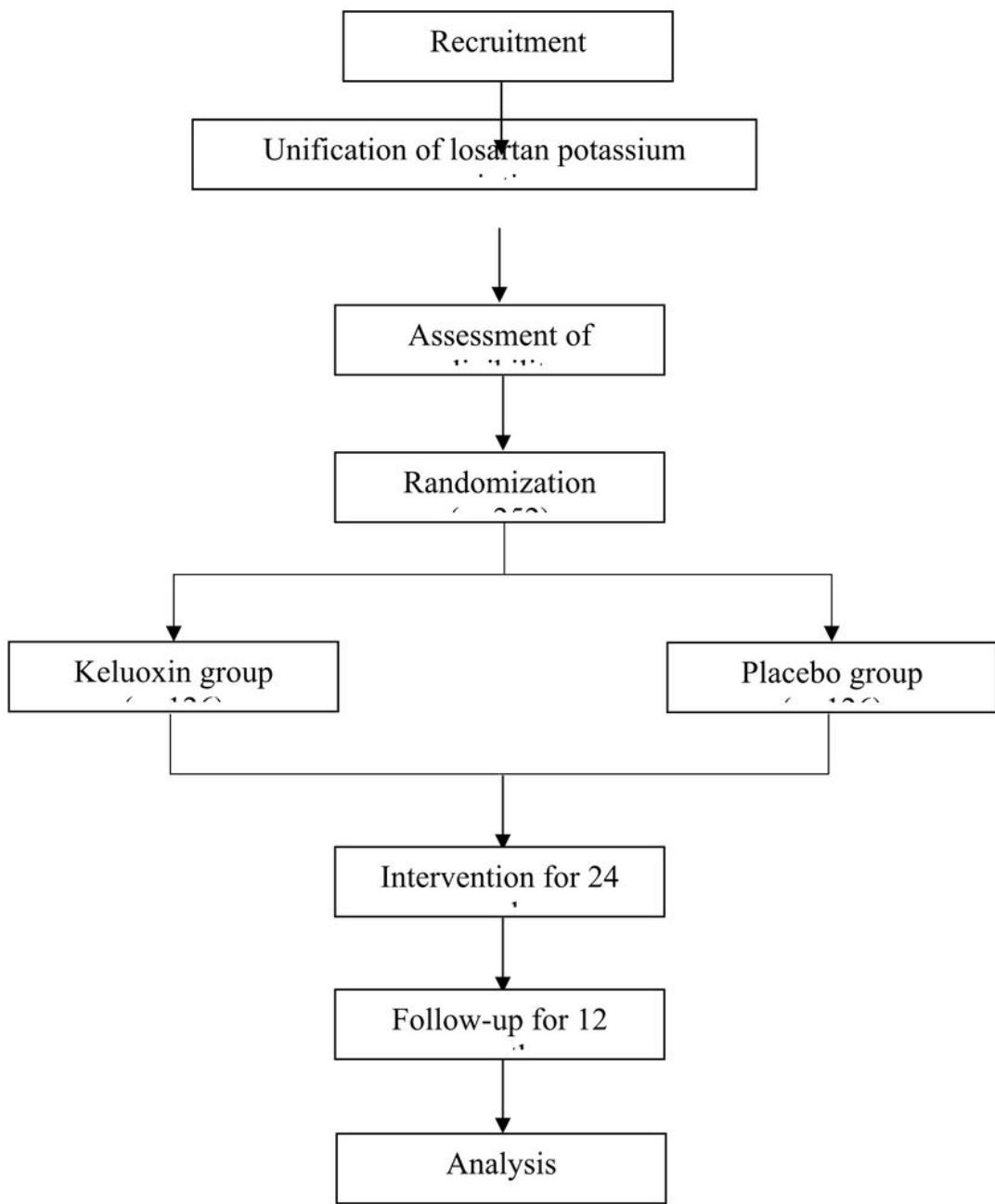


Figure 1. Trial flow chart.

Figure 1

A flowchart of the study design

Supplementary Files

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