

Study Protocol

Protocol on Comparative efficacy of *Bruhatyadi Kwath* as compared to Furosemide for improving e-GFR and Albuminuria in Chronic Kidney Disease.

ABSTRACT:

Background: The steady decrease of kidney function is referred to as chronic kidney disease. The kidney function is measured by Golmerular Filtration Rate (GFR). According to Ayurveda the CKD can be correlated to *Mutraghata* because of similarity of symptoms. In Ayurveda *Mutraghata* is described under *Mutraroga* which comes under *Mutravahastrotas* (urinary system). **Objective** – To access and compare the efficacy of *BruhatyadiKwath*, furosemide and *BruhatyadiKwath* along with furosemide on symptoms, eGFR, and Albuminuria in various stages of Chronic Kidney Disease. **Methodology** – Total 90 patients will be divided in 3 equal groups. Patients in group A will be treated with *Bruhatyadikwatha*, group B patients will be treated with furosemide and patients in group C will be treated with *BruhatyadiKwatha* and furosemide for 90 days. Follow up will be taken after every 30 days. **Expected results** – Furosemide along with *Bruhatyadikwath* will show better improvement in e-GFR and Albuminurea as compare to only treated with *Bruhatyadikwath* and furosemide. Assessment of subjective criteria like Edema, Anorexia, weakness and vomiting will be done on day 0, 30, 60 and 90 whereas assessment of Serum creatinine, Blood Urea, Sr. Sodium, Sr. Potassium, eGFR (Cockcroft formula) and Albuminuria will be done before and after treatment (on 0 and 90th day). **Result:** Subjective and objectives outcomes will be assessed by statistical analysis. **Conclusion:** It will be drawn from the result obtained.

Keywords – e- GFR, CKD, Albuminurea, *Mutraghata*, *Bruhatyadikwath*, Furosemide

INTRODUCTION –

Chronic Kidney Disease (CKD) is a progressive, permanent decline in kidney function that usually occurs over months to years. It begins as a biochemical aberration, but when the kidney's excretory, metabolic, and endocrine functions deteriorate, clinical signs and symptoms of renal failure, commonly known as uraemia, develop. End Stage Renal Disease (ESRD) is a term used to describe a condition in which mortality is likely without RRT (Renal Replacement Therapy) (CKD stage 5)¹.

Chronic Kidney Disease (CKD) is becoming a major chronic disease worldwide. One reason is that the global incidence of diabetes and hypertension is quickly growing. Given India's population of over one billion people, the increased frequency of CKD is projected to cause severe challenges in the future for both healthcare and the economy. Indeed, the age-adjusted incidence rate of end-stage renal illness in India has recently been estimated to be 229 per

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million people, with more than 100,000 additional patients entering renal replacement programmes each year². Only 10% of Indian patients with end-stage renal disease receive any renal replacement therapy due to a lack of funding.

Therefore, exploration of a safe and alternative cost-effective therapy is highly required, which proves to be helpful in reducing requirement or frequency of dialysis and in postponing the renal transplantation.

Chronic kidney disease (CKD) is a kind of kidney disease in which kidney function gradually deteriorates over months to years.

Kidney function is a measure of the kidney's health and its contribution to renal physiology.

The glomerular filtration rate (GFR) is a metric for measuring kidney function.

The Glomerular Filtration Rate (GFR) is the rate at which filtered fluid flows through the kidneys. Without Chronic Kidney Disease, a Glomerular Filtration Rate (GFR) of 60 ml/min/1.73 m² is considered normal³. Chronic Kidney Disease is characterised as having a GFR of less than 60 ml/min/1.73 m² for three months. In CKD we get changes in blood, urine and imaging studies. In blood there is raised sr. Creatinine & urea even than normal Albuminuria in urine is the oldest and widely used marker for kidney dysfunction, Albumin is the most prevalent plasma protein, and its urine excretion is determined by the combined effects of glomerular filtration and renal tubular processing. It's also used to track CKD progression. On the basis of GFR, Chronic Kidney Disease (CKD) is divided into five stages.

The majority of patients with slowly progressive illness are asymptomatic until their GFR drops below 30 ml/min/1.73 m², and others can be asymptomatic even with significantly lower GFR values.

Symptoms and indicators are typical when GFR goes below 15-20 ml/min/1.73m², and they can influence practically all physiological systems⁴. Tiredness or shortness of breath, as well as lower limb swelling, can all be signs of renal anaemia or fluid overload.

Patients with worsening renal function may have pruritus, anorexia, weight loss, nausea, vomiting, and hiccups.

Due to significant metabolic acidosis, the patient's respiration may be exceptionally deep (Kussmaul breathing) in very severe renal failure and muscle twitching, fits, sleepiness, and coma are all possible side effects⁵.

Ayurvedic management has proved its potential as an alternative medicine for the treatment of a variety of ailments in recent years, and it continues to be a key source for the discovery of new medications, which has gotten more attention recently. Ayurvedic therapy is also becoming more popular for enhancing healthcare and preventing Chronic Kidney Disease, according to data (CKD). Chronic Kidney Disease is not described in *Ayurveda* but due to similarity of symptoms it can be correlated with *Mutraghata*, which is one of the most important *Mutraroga* as described in ancient Samhitas. There are a variety of formulations available that target urinary system problems and have a variety of activities. *Brihatyadikwatha* is one of them described in Sushruta Samhita⁸. It contains *Gokshur*, *Brihati*, *Patha*, *Indrayava*, *Kantakari* and *Yashtimadhu* as shown in table no. 1. All these herbs have *mutral* (Diuretic) property. In Sushruta Samhita *BruhatyadiGana* is mainly described for the management of *Mutrakruccha* where as in Sahastryogam it is indicated in the management of all *Mutravikara*⁶. It possesses *Rasayana* property which is helpful in regeneration of damaged kidney. *Deepan-Pachan* property of these drugs reduces production of *Aam* as well as *Kleda*. It corrects *Mansa* and *Medadhatwagni* by its *Katu*, *Tikta Rasa* and *Ushna Veerya* thus reduces production of *Kha-Mala*.

Rationale of the study:

Chronic kidney disease (CKD) is a global health problem that costs health systems a lot of money, and it's also a risk factor for cardiovascular disease (CVD).

CKD is linked to an increased risk of cardiovascular morbidity, premature mortality, and/or a lower quality of life at all stages. In modern science management of Chronic kidney disease mainly includes supportive treatment, use of diuretics and in severe cases dialysis or renal transplant. But all these treatment has their own limitations like high cost, adverse effects as well as complications. In *Ayurveda* many herbal formulations having *Mutral* (diuretic) and *Rasayana* (rejuvenating) properties are recommended in the management of *Mutravikar* as like *Mutraghata* (chronic kidney disease). Various research studies conducted on herbal drugs in *mutravikaras* are available showing their efficacy^{7,8,9}. *BruhtyadiKwath* possesses diuretic, rejuvenating, antibacterial and anti-inflammatory properties. Research studies are conducted on *BruhatyadiKwath* in the management of *Mutrakruchra* but no study conducted on *Mutraghata*¹⁰. So for early stage prevention and to check further progression this study is planned along with furosemide to evaluate the efficacy of *Bruhtyadi Kwath* for improving e-GFR and Albuminuria in Chronic Kidney Disease.

Aim and Objectives:**Aim**

Comparative efficacy of *BruhatyadiKwath* as compare to Furosemide for improving e –GFR and Albuminuria in Chronic Kidney Disease.

Objectives:**(a) Primary objective:**

- To access the efficacy of *BruhatyadiKwath* on symptoms, eGFR, and Albuminuria in Chronic Kidney Disease.
- To access the efficacy of *BruhatyadiKwath* with furosemide on symptoms, eGFR, and Albuminuria Chronic Kidney Disease.
- To access the efficacy of furosemide on symptoms, eGFR, and Albuminuria in Chronic Kidney Disease.
- To compare the effect of above therapy in various stages of Chronic Kidney Disease.

Case definition-

Patients having age ≥ 20 years of either sex having eGFR ≥ 90 to 30 (Cockcroft formula) that is Chronic Kidney Disease of stage 1 to 3 with albuminuria will be included in the study.

Research Question-

Whether *BrihatyadiKwath* + furosemide is effective as compare to *BrihatyadiKwath* and furosemide in improving e-GFR and Albuminuria in Chronic kidney Disease?

Comment [u4]: Mention the term clearly what you are supposed to do.

Hypothesis:**(a) Null Hypothesis (H0):**

BruhatyadiKwath + furosemide may not be more effective than *BruhatyadiKwath* and furosemide in improving the e-GFR and Albuminuria in Chronic Kidney Disease (CKD)

(b) Alternative Hypothesis (H1):

BruhatyadiKwath + furosemide may be more effective than *BruhatyadiKwath* and furosemide in improving the e-GFR and Albuminuria in Chronic Kidney Disease (CKD)

(c)Component of Hypothesis

1] Estimated Glomerular filtration Rate by Chronic Kidney Disease Epidemiology Equation (eGFR-EPI) and Albuminuria is useful marker to assess the progress in Chronic Kidney Disease and efficacy of *BruhtyadiKwath*¹¹.

2]. Duration of 3 months is sufficient to prove the efficacy of *BruhatyadiKwath*.

3]. Dose of 40 ml twice a day is adequate for the desired effect.

Trial design: randomized reference controlled clinical trial

METHODOLOGY:

Study setting:

Patients of chronic kidney disease (CKD)will be selected from OPD and IPD of Mahatma Gandhi Ayurved College, Hospital and Research centre (MGACH & RC), Salod (H), Wardha, and Jawaharlal Nehru Medical College (JNMC), Sawangi (Meghe).

CTRI Ref. Number: The clinical study is registered to Clinical Trial Registry and reference no is REF/2021/05/043802

Study Formulation (*BruhtyadiKwatha*) contents-

BruhtyadiKwatha will be freshly prepared each time by Standard operating procedure mentioned in Sharangadhara Samhita

Comment [u5]: Detail reference for Intervention included

Table no.1 *BruhatyadiKwath* ingredients-

Sr.	Drug name	Botanical Name	Part Used	Relative Quantity
1.	<i>Bruhati</i>	<i>Solanum indicum</i> Linn.	<i>Mula</i> (Root)	Equal
2.	<i>Kantakari</i>	<i>Solanumsurrattense</i> .Burm.	<i>Phal</i> (Fruit)	Equal
3.	<i>KutajbeejaIndrayava</i>	<i>Holarrhenaantidysentrica</i> .Linn	<i>Beej</i> (seed)	Equal
4.	<i>Patha</i>	<i>Cissampelospariera</i> .Linn	<i>Mula</i> (Root)	Equal
5.	<i>Yastimadhu</i>	<i>Glycyrrhizaglabra</i> Linn.	<i>Kand</i> (Stem)	Equal
6.	<i>Gokshur</i>	<i>Tribulusterrestris</i> .Linn	<i>Phal</i> (Fruit)	Twice of above all

Eligibility criteria:

Inclusion Criteria

1. Age ≥ 20

Comment [u6]: Also mention the lower limit of age

2. Diagnosed patients of Chronic Kidney Disease (Best on eGFR, and Albuminuria)

- Clinically stable patients of stage 1 to 3 will be included
 Stage 1- GFR ≥ 90 (Cockcroft formula)
 Stage 2- GFR between 60 to 89.
 Stage 3 3a: e GFR (EPI) 45 to < 60
 3b: e GFR (EPI) 30 to < 45

3. Albuminuria.

Exclusion Criteria

1. Postrenal transplant.
2. Known case of HIV patients or subjects on immune suppressive drugs.
3. Pregnant and lactating females.

Comment [u7]: What about associated systemic diseases?

3.4] Interventions of groups: Table no.2

Group	Sample size	Intervention	Dose and frequency	Duration	Follow up
Group-A	30	<i>BruhtyadiKwath</i>	40 ml (BD) Morning & Evening After meal	3 months	Monthly
Group-B	30	Furosemide+ <i>BruhtyadiKwath</i>	40mg OD 10am + 40 ml (BD) Morning & Evening After meal	3 months	Monthly
Group- C	30	Furosemide	40 mg OD 10 am	3months	Monthly

Criteria for discontinuing or modifying allocated interventions:

1. Discontinuation of Drug during trial.
2. Participants developing life threatening complication.
3. Development of any non related ailments which may require other medications.

Follow up: on 30th, 60th and 90th day.

Primary Outcomes: Outcome of Both the Treatment will be seen in –

- 1.Changes in albuminuria from baseline
- 2.Changes in eGFR from baseline
3. Fraction of patients with improved eGFR of more than 25%
4. Proportion of participants achieving up to 50% reduction from baseline albuminuria.
5. Fraction of patients reverted to stage 2[eGFR(EPI)-60 to 89] from stage 3 [eGFR (EPI)-45 TO 60] or from stage 3b[eGFR(EPI)-30 to <45] to stage 3a [eGFR(EPI)-45 to <60]
6. Increase in time interval for progression to grade 4 [eGFR(EPI)-15 to 29] from grade 3 or from grade 3a to grade 3b.

Sample Size : For calculating sample size with desired error of margin-

$$n = \frac{Z_{\alpha/2}^2 \times P \times (1-P)}{d^2}$$

Where,

$Z_{\alpha/2}$ is the level of significance at 5% i.e 95% confidence interval=1.96

P = Expected Response Rate = 5%= 0.05

D=Derived error of margin=7%=0.06

$$n = \frac{1.96^2 \times 0.05 \times (1-0.05)}{0.06^2}$$

= 25.86 $n = 30$ patients needed in each groups.

Statistical analysis: The observations will be analyzed by using chi square test and student unpaired t test.

Time duration till follow up: The patient will be followed up during treatment of 30, 60, 90th days.

Time schedule of enrolment, interventions: Drug will be given from 0 to 30 days

Recruitment: patient will be recruited by Computerised algorithm for random allocation into three groups of 90 (30 patients in each group).

5]Methods:

5.1]Data collection methods: Assesment criteria:

SUBJECTIVE CRIETERIA:

Gradation of Subjective Criteria Table no.3

Assessment of subjective criteria like Edema, Anorexia, weakness and vomiting will be done on day 0, 30, 60 and 90.

Sr.No	Symptom	Grade 0	Grade 1	Grade 2	Grade 3
1	Edema	Absent	Mild both ankle feet	Moderate both feet, hands, lower arms and legs	Early morning puffiness
2	Anorexia	Normal instinct for food	Seek for food but refuses	Does not seek for food	Intense havoc n taste dislikes even sight and smell of food
3	Weakness	No	Weakness on strenuous work	Weakness on slight work but relieved soon	Weakness on slight work relieving over period of time
4	Vomiting	Absent	Sensation only for food of dislike	Vomiting few episodes <5	Vomiting episodes >5

Comment [u8]: Mention the timeline correctly with total study period, recruitment, treatment period, follow up, statistical analysis period.

Comment [u9]: If it is a randomized study mention it clearly in the title.

OBJECTIVE CRITERIA:

- 1. Serum creatinine.
- 2. Blood Urea
- 3. Sr. Sodium
- 4. Sr. Potassium
- 5. eGFR (Cockcroft formula)
- 6. Albuminuria

} will be done before and after treatment

Data management: The data entry coding will be done by PI

Statistical methods: The observations will be analyzed by using chi square test and student unpaired t test.

Ethics and dissemination: Research ethics approval; approval from research ethics committee has taken. Ref. No.-MGACHRC/IEC/February-2021/188

Consent or assent: The written consent will be taken from the patient before starting the study. During the study the confidentiality of each patient will be maintained.

Dissemination policy: The data will be disseminated by paper publication.

Guidelines for authorship eligibility, as well as any planned employment of professional writers

Informed consent materials: With all the information consent form and other related documentation will be given to participants.

Strengths: Furosemide is known loop diuretic drug used in CKD, if *BruhadyadiKwath* is given along with it may found effective in alleviating the subjective and objective parameters. So the use of two drugs in combination will have significant effect on preventing progression of CKD and correcting albuminuria in early stages.

Limitations: This study will not be conducted on major systemic diseases and also in advanced stages of stage 4 and 5.

Comment [u10]: Mention it in exclusion criteria

Chart 1. Gantt chart (in quarterly based)

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Literature search	█										
preparing study material	█	█									
Validation of study material			█	█							
Study intervention					█	█					
Data collection & Analysis							█	█	█	█	
Thesis writing										█	█

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