Protocol on Comparative Efficacy of *Bruhatyadi Kwath* as Compared to Furosemide for Improving e–GFR and Albuminuria in Chronic Kidney Disease- A Randomized Controlled Study

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Authors’ contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Study Protocol

ABSTRACT

**Background:** The steady decrease of kidney function is referred to as chronic kidney disease. The kidney function is measured by Glomerular Filtration Rate (GFR). According to Ayurveda the CKD can be correlated to Mutraghata because of similarity of symptoms. In Ayurveda Mutraghata is described under Mutrarogawhich comes under Mutravahastrotas (urinary system).

**Objective:** To assess and compare the efficacy of Bruhatyadikwath, Furosemide and Bruhatyadikwath along with Furosemide on symptoms, eGFR, and Albuminuria in various stages of Chronic Kidney Disease.

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Methodology: Total 90 patients will be divided in 3 equal groups. Patients in group A will be treated with Bruhatayadikwatha, group B patients will be treated with Furosemide and patients in group C will be treated with Bruhatayadikwatha and Furosemide for 90 days. Follow up will be taken after every 30 days.

Expected Results: Furosemide along with Bruhatayadikwath will show better improvement in e-GFR and Albuminurea as compared to only treated with Bruhatayadikwath 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 objective outcomes will be assessed by statistical analysis.

Conclusion: It will be drawn from the result obtained.

Keywords: Albuminuria; Bruhtyadi kwath; e-GFR; CKD; furosemide; Mutraghat.

1. 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 million people, with more than 100,000 additional patients entering renal replacement programmes each year [2]. 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 normal [3]. 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 Serum Creatinine and 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 systems [4]. 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 effects [5].
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 Samhita. It contains Gokshur, Brihati, Patha, Indrayava, Kantakari and Yashtimadhu as shown in Table 1. All these herbs have Mutral (Diuretic) property. In Sushruta Samhita Bruhatyadigana is mainly described for the management of Mutrakruccha whereas as in Sahastrayogam it is indicated in the management of all Mutravikara. It possesses Rasayana property which is helpful in regeneration of damaged kidneys. 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.

1.1 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 treatments have 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 [8,6,9]. Brihatyadikwatha possesses diuretic, rejuvenating, antibacterial and anti-inflammatory properties. Research studies are conducted on Bruhatyadikwatha in the management of Mutrakruccha but no study is 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 Bruhtyadikwath for improving e-GFR and Albuminuria in Chronic Kidney Disease.

2. AIM AND OBJECTIVES

2.1 Aim

Comparative efficacy of Bruhatyadikwath as compared to Furosemide for improving eGFR and Albuminuria in Chronic Kidney Disease.

2.2 Objectives

(a) Primary objective:
- To assess the efficacy of Bruhatyadikwath on symptoms, eGFR, and Albuminuria in Chronic Kidney Disease.
- To assess the efficacy of Bruhatyadikwath with Furosemide on symptoms, eGFR, and Albuminuria Chronic Kidney Disease.
- To assess 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.

2.3 Case Definition

Patients having age ≥ 20 to 70 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.

2.4 Research Question

Whether Brihatyadikwath along with Furosemide is effective as compared to Brihatyadikwath and Furosemide given separately in improving e-GFR and Albuminuria in Chronic kidney Disease?

2.5 Hypothesis

(a) Null Hypothesis (H0):

Bruhatyadikwath along with Furosemide may not be more effective than Bruhatyadikwath and Furosemide given separately in improving the e-GFR and Albuminuria in Chronic kidney Disease (CKD)
(b) Alternative Hypothesis (H1):

BruhatyadiKwath along with Furosemide may be more effective than Bruhatyadikwath and Furosemide given separately 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 a useful marker to assess the progress in Chronic Kidney Disease and efficacy of Bruhatyadikwath [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.

[4] Trial design: randomized reference controlled clinical trial

3. METHODOLOGY

3.1 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

3.2 Study Formulation (Bruhtyadi kwatha) Contents

Bruhtyadikwatha will be freshly prepared each time by Standard operating procedure as per the reference of Sharangadhar Samhita (Madhyam Khanda 2/1 and 8/1). In coarse powder of raw material 16 parts of water will be added and it will be heated to reduce to 1/8 part. Mixture will be filtered and decoction will be obtained.

3.3 Eligibility Criteria

Inclusion Criteria

1. Age ≥ 20 to 70 years
2. Diagnosed patients of Chronic Kidney Disease (Best on eGFR, and Albuminuria)
3. 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. Known cases of uncontrolled diabetes mellitus, hypertension, heart diseases, and cancer
4. Pregnant and lactating females.

3.4 Criteria for Discontinuing or Modifying Allocated Interventions

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

Table 1. BruhatyadiKwath ingredients

| Sr. | Drug name | Botanical Name | Part Used | Relative Quantity |
|-----|-----------|----------------|-----------|------------------|
| 1.  | Bruhati   | Solanum indicum Linn. | Mula (Root) | Equal |
| 2.  | Kantakari | Solanum suurrattense.Burm. | Phal (Fruit) | Equal |
| 3.  | KutajbeejIndrayava | Holarrhena antidysentrica.Linn | Beej (seed) | Equal |
| 4.  | Patha     | Cissampelospariera.Linn | Mula (Root) | Equal |
| 5.  | Yastimadhu| Glycyrrhizaglabra.Linn | Kand (Stem) | Twice of above all |
| 6.  | Gokshur   | Tribulusterrestris.Linn | Phal (Fruit) | Equal |
Table 2. Interventions of groups 3.4

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

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)-60 to 89] or from stage 3b[eGFR(EPI)-45 TO 89] 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.

3.5 Sample Size

For calculating sample size with desired error of margin-

\[ \eta = \frac{Z_{\alpha/2} \times P \times (1 - P)}{d^2} \]

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

\[ \eta = \frac{1.962 \times 0.05 \times (1 - 0.05)}{0.06^2} = 25.86 \]

\( \eta \) = 30 patients needed in each groups.

3.6 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 treated for a total 90 days and will be followed up on day 30, 60, 90.

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

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

3.7 Methods

3.4.1 Data collection methods: Assessment criteria

Subjective Criteria:

Obective Criteria:

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

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

4. DISCUSSION

In Chronic kidney disease, the kidney functions gradually go on decreasing due to various pathologies. It reduces excretion of waste products formed during metabolism, increases leakage of proteins and electrolytes due to damage of nephrons. This loss of proteins, electrolytes depletion and accumulation of nitrogenous waste products produces symptoms. As per Ayurveda, Mutraghata means retention of urine along with pain in supra pubic region are observed due to obstructive pathology, there is deranged function of Vatadosha, particularly anapanavata which is the prime causative factor also vitiating Kaphadosha, affecting to mutravahasrotas and derangements occurs in Basti which results in Mutraghata. In this study patients will be divided in three equal groups and will be given interventions as shown in Table 2. The contents of BruhatyadiKwatha having Vata-Kapha pacifying, Srotoshodhana, Shothahara, Mutral, and Deepana Pachana (appetizer and digestive) properties which help in breaking samprapti of Mutraghata. The combination of these drugs possesses the Rasayana (rejuvenating) property as it contains Gokshura and Yashtimadhu [12]. Due to Rasayana property it will promote and boost cell growth and their function. It acts as a Kaphaghna because of Tiktakatu rasa. It also acts as Kledashoshak because of the Grahiguna of Indrayava and Brihati. Srotovishodhana as it contains Patha and Kantakari and lastly it has Mutral property because of Gokshur. In this way Brihatyadikwath helps in breaking pathogenesis.

The herbal drugs having Mutral property are useful in Mutraghata is also proved by various research studies [13,14,15]. A number of studies on different aspects of Chronic Kidney Diseases were reported [16-20]. Few of the related studies were reviewed [21-25].

Furosemide is a loop diuretic that is used to treat hypertension and edema in people with
congestive heart failure, liver cirrhosis, renal illness, and high blood pressure. Diuretics enhance urine salt and water excretion by inhibiting sodium reabsorption in particular renal tubules. It is a drug used in CKD. The subjective criteria as shown in Table 3 and objective criteria will be assessed before and after treatment.

5. CONCLUSION

Conclusion will be drawn after statistical analysis.

6. RECOMMENDATION

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

7. LIMITATIONS

This study will not be conducted on major systemic diseases like uncontrolled diabetes mellitus, hypertension, malignance and immunocompromised disorders and also in advanced stages of stage 4 and 5.

CONSENT

The written consent will be taken from the patient before starting the study. During the study the confidentiality of each patient will be maintained. With all the information consent form and other related documentation will be given to participants.

ETHICAL APPROVAL

Research ethics approval; approval from the research ethics committee has taken. Ref. No.- MGACHRC/IEC/February-2021/188

DISSEMINATION POLICY

The data will be disseminated by paper publication.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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