



Topical Application of Glycerine – Paraffin Combination in CKD-associated Pruritus and Uremic Xerosis: Study Protocol for a Randomized Control Trial

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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

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ABSTRACT

Background: Chronic kidney disease associated pruritus (CKD-ap) and xerosis is intensely annoying and unpleasant manifestations associated with maintenance renal dialysis (MRD) among chronic kidney disease (CKD) patients. It severely compromises the quality of life by disturbing normal sleep pattern and also adversely affect the mental health in CKD patients. Many proposed treatment plan for CKD –ap is tested but none of the treatment plan provide complete relief from itch associated with MRD. Glycerine accelerate barrier repair and also has rapid hydrating and smoothing effect while Paraffin preserve the barrier function against irritant. As a comparator Mustard oil is used as it is commonly used home remedy by people in Indian sub-continent for dry skin.

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Objectives: The primary objective of the study is to compare the efficacy of Glycerine –paraffin combination with mustered oil on skin related quality of life among CKD patients with CKD-ap and xerosis.

Methodology: A randomised, single blind, controlled, clinical trial intending to investigate and compare the efficacy of Glycerine – Paraffin combination with mustard oil in CKD –ap and xerosis and overall SRQOL among CKD patients. The study aims to enrol 140 CKD patients having moderate to severe CKD-ap and xerosis by using GI gammal score (standardized tool for assessment of xerosis). They will be randomly distributed among 2 parallel group, experimental & control group. Allocation concealment will be maintained by using SNOSE technique. Experimental group will be instructed to apply glycerine paraffin combination and mustard oil to control group twice a day for 4 weeks. participant will be evaluated for xerosis and pruritus score at baseline, day 7, day 28 and day 56. Scores of SRQOL will be assessed at baseline and on 56 days.

Conclusion: The RCT aims to identify & compare the efficacy of Glycerine –paraffin combination with mustard oil on skin related quality of life among CKD patients with CKD-ap and xerosis.

Keywords: CKD (Chronic kidney disease); MRD (Maintenance renal dialysis); CKD-ap (Chronic kidney disease associated pruritus); Xerosis; SRQOL (skin related quality of life).

1. INTRODUCTION

Incidence of end stage renal disease (ESRD) has increased exponentially during the last 30 years and prevalence is increasing in many countries. From 27th commonest cause of death globally, it climbed the ladder to 18th position in 2010 (Global burden of disease study 2010) [1]. CKD patients often suffer from many skin manifestations spanning from generalized xerosis and pruritus to less common manifestations like purpura, skin discolouration of exposed body parts, nail changes and acquired perforating dermatosis [2]. Xerosis (rough and scaly skin) frequency significantly increases in end-stage renal disease patients as soon as they start on maintenance renal dialysis (MRD), sometimes it is also present in CKD patient before dialysis [3-4]. In majority of patient it disappears after renal transplant [5]. Uremic pruritus is very common and disabling symptoms among patient with ESRD. Uremic xerosis and uremic pruritus goes hand in hand. Uremic xerosis may provoke or accelerate the irritating symptoms of pruritus. Owing to its complex and multifactorial pathophysiology it is very difficult to eradicate but the symptoms can be alleviated [4,6].

A notable positive association was established amid the xerosis intensity and prevalence of pruritus by Sczepietowski et al. [5]. They Studied the intensity of pruritus on 130 patient with chronic renal failure and on maintenance renal dialysis by using visual analogue scale and questionnaires scoring method. It was reported that 40.8% samples were suffering from uremic pruritus, another 36.1 percent patients reported

having pruritus in past. Itching was generalized in 19% of the patient, (50%) reported having dispersed pruritus, and (31%) reported pruritus in a single location [5]. The course of uremic pruritus is extended, recurrent and severe having negative influence on the quality of life. The major factors escalating pruritus include rest, heat, dry skin and sweat. whereas activity reduces the pruritus [7]. The management of chronic kidney disease associated pruritus poses a grave treatment challenge because of unavailability of effective therapeutic regimen. It has been recommended that treatment of chronic kidney disease associated pruritus should be undertaken according to individuals benefit risk ratio assessment [8].

There is intense need for better skin management for itch in patient with end stage renal disease or chronic kidney disease. Moisturization of skin and modification of lifestyle are indispensable factors to minimise dermtological menifestations associated with renal disease [9]. A survey done by Weisssharr et.al on how do nephrologist in hemodialysis unit considered the symptoms of itch. It was reported that the prevalence of up may be misjudged by nephrologist. The undulating pattern of CKD-ap after dialysis may interfere with the recognition of CKD –ap leading to large variation in its reported prevalence further they reported that no substantial difference in recognition and management of CKD-ap is identified [10].

Mathur et al. [11] reported in his longitudinal study that 84% of people reported itch on daily basis or nearly daily and it is continued for more

than 1 year in 59%. Pruritis was observed with bilateral symmetry involving large, non-dermatomal areas in 83% of people. In spite of using medications such as antihistamines, steroids and various emollient there was no satisfactory relief of itching. Health related quality of life measures were positively associated with changes in intensity of itch of 20% or more among patient with moderate to severe CKD-ap.

Dhabi et al. [12] states that the cutaneous manifestation in hemodialysis patients deserves a proper management by both dermatologist and nephrologist to improve the quality of life among ESRD patients.

2. RATIONALE OF STUDY

Many proposed treatment plan for CKD -ap is tested but none of the treatment plan provide complete relief from itch associated with MRD. Glycerine accelerate barrier repair and also has rapid hydrating and smoothing effect while Paraffin preserve the barrier function against irritant. The Glycerine and Paraffin has been tested separately and reported effective for the target indication in previous studies. The investigator wants to assess its efficacy in combination for uremic xerosis and CKD-ap [13].

As a comparator Mustard oil is used as it is commonly used home remedy by people in Indian sub-continent for dry skin. Mustard oil is a natural plant oil extracted from Brassica nigra & B. Hurta and very commonly used as topical therapy for dry skin in south Asia. It is easily available and relatively in expensive than other plant oils and popularly used home remedy by people in Indian subcontinents for skin moisturization although its efficacy and safety is yet to establish [14-15]. It contains 12% oleic acid, 15% linoleic acid & 75% other fatty acids [14]. Oil with higher linoleic acid to oleic acid ratio have better repairing ability comparing to oil with high oleic acid percentage [15].

3. OBJECTIVES

1. To assess the baseline xerosis, uremic pruritus and SR- QOL in experimental & control group of CKD patient.
2. To assess the effectiveness of mustard oil on xerosis, CKD associated uremic pruritus (CKD -ap) and SR-QOL in control group of CKD patients.
3. To assess the effectiveness of Paraffin and Glycerine combination on xerosis, CKD

associated uremic pruritus (CKD -ap) and SR- QOL in experimental group of CKD patients.

4. To compare the effectiveness of glycerine - Paraffin combination with Mustard oil in management of CKD associated uremic pruritus (CKD-ap), xerosis and SR-QOL.

Trial design: This is a prospective, single blind, parallel group controlled, Randomized clinical trial.

4. METHODOLOGY

Study setting: The study setting is dialysis units, in patient department (IPD) or Nephrology OPD of Acharya Vinoba Bhave Rural hospital Sawangi (Meghe), Wardha, MH.

4.1 Eligibility Criteria

4.1.1 Inclusion criteria

Study will have samples confirmed to the following criteria.

- CKD patient having moderate to severe uremic xerosis & between age group of 18 -65 years.
- Patient who can understand Marathi / Hindi/ English.
- Those who all are willing to participate in the study and are available at the time of data collection.

4.1.2 Exclusion criteria

- CKD patients who are critically ill.
- CKD patient on any type of skin treatment or systemic drug for management of uremic xerosis & CKD -ap.

Interventions: A randomised, single blind, controlled, clinical trial with concealed allocation by SNOSE technique is designed to investigate and compare the efficacy of Glycerine – Paraffin combination with mustard oil in CKD -ap and xerosis and overall SRQOL among CKD patients. The study aims to enrol 150 CKD patients with moderate to severe CKD-ap and xerosis by using GI gammal score. They will be randomly distributed among 2 parallel group, experimental & control group. Experimental group will be instructed to apply glycerine Paraffin combination and Mustard oil to control group twice a day for 4 weeks. Participant will be

evaluated for xerosis and pruritus score at baseline, day 7, day 14, day 28 and day 56. Scores of SRQOL will be assessed at baseline and on 56 days.

Participants allocated to the experimental or control group will be instructed to take bath/wash the skin with water or wet cloth and pat the skin dry. For bathing they should use mild soap (low fragrance) and Luke warm water and limit the bathing time to less than 10 minute. Any type of vigorous rubbing of skin should be avoided They will be instructed to apply the provided emollient all over the body liberally, twice a day morning after bath and night before going to bed by gentle massage with finger pads.

The participants will be instructed to maintain a diary entry for the application to improve adherence to treatment protocol. They are also asked to report any adverse reaction like worsening of symptoms and also to return the empty bottles.

Use of any other dermatological preparations/systemic therapy for CKD-ap & xerosis is strictly prohibited during the trial.

4.1.3 Outcomes

Primary outcome: The primary outcome will be measured by changes in scores of xerosis & uremic pruritus. The measurement of xerosis & uremic pruritus will be done at baseline & on 7th, 14th, 28th & 56 day. Subjective measurement of pruritus will be done on 1 -10 VAS scale.

Secondary outcome: Secondary outcome measurement will be measured by changes in scores of SRQOL using dermatological index at baseline, on 28th & 56th day.

Safety outcome measurement: The documented allergic reaction with glycerine on topical application are redness, itching and burning and of mustered oil are itching, redness, skin irritation etc. Paraffin has no documented side effects [13,15].

Dermal tolerability of product will be checked by applying it in a small area. Investigator will assess & documents the adverse side effect encountered by the patient.

Participant timeline: the study is divided in two phase; in phase I consists of topical treatment of 1 month & phase II consists of follow-up for

another 1 month. Visits are planned on 0,1,7,14,28 & 56th day.

Sample size: Sample size was calculated using the formula when outcome measure is continuous variable. The approximate number of participants needed to achieve study objectives is 70 participants in each group (control & experimental) so total sample size is 140. Taking in to consideration the 10% of dropout rate the total sample size would be 154. The formula used for sample size calculation is as follows

$$n = 2 \left[\frac{z_{\alpha} + z_{\beta}}{d} \right]_x^2 \sigma^2$$

Where Z_{α} = 90% of confidence interval
 Z_{β} = 80% of power of size
 d = effect size of continuous variable
 σ = standard deviation for continuous variable

To recruit the patient for study initially I will contact the patients with Patient IPD. No./OPD no. followed by screening of patient for xerosis using GI gammad scoring. Those who will fall in category of moderate & severe xerosis will be assigned to control & experimental group by keeping the allocation concealed using SNOSE technique.

Methods: Assignment of interventions (for controlled trials): Sequentially numbered, opaque, sealed envelopes will be used for Mechanism of implementing the allocation sequence. Trial participant will be blinded (single blinding) by concealing the allocation to experimental or control group. unblinding is not permissible in this study.

Data collection, management, and analysis methods: Baseline & other trial data will be collected using 3 standard instruments. Modified EI Gammad scoring (0 = smooth skin; 1= patches of fine powdery scales; 2 = diffuse ashy appearance with many fine scales; 3 = moderate scaling with beginning of cracks; 4 = intense scaling with moderate cracks) will be used to assess the severity of xerosis before & after intervention. Dermatological quality of life index will be used to assess Skin related quality of life. Visual analogue scale will be used to assess subjective itch intensity.

Data will be collected from additional 10% participants in view of dropouts. Regular follow up visit will be made by investigator to facilitate better retention.

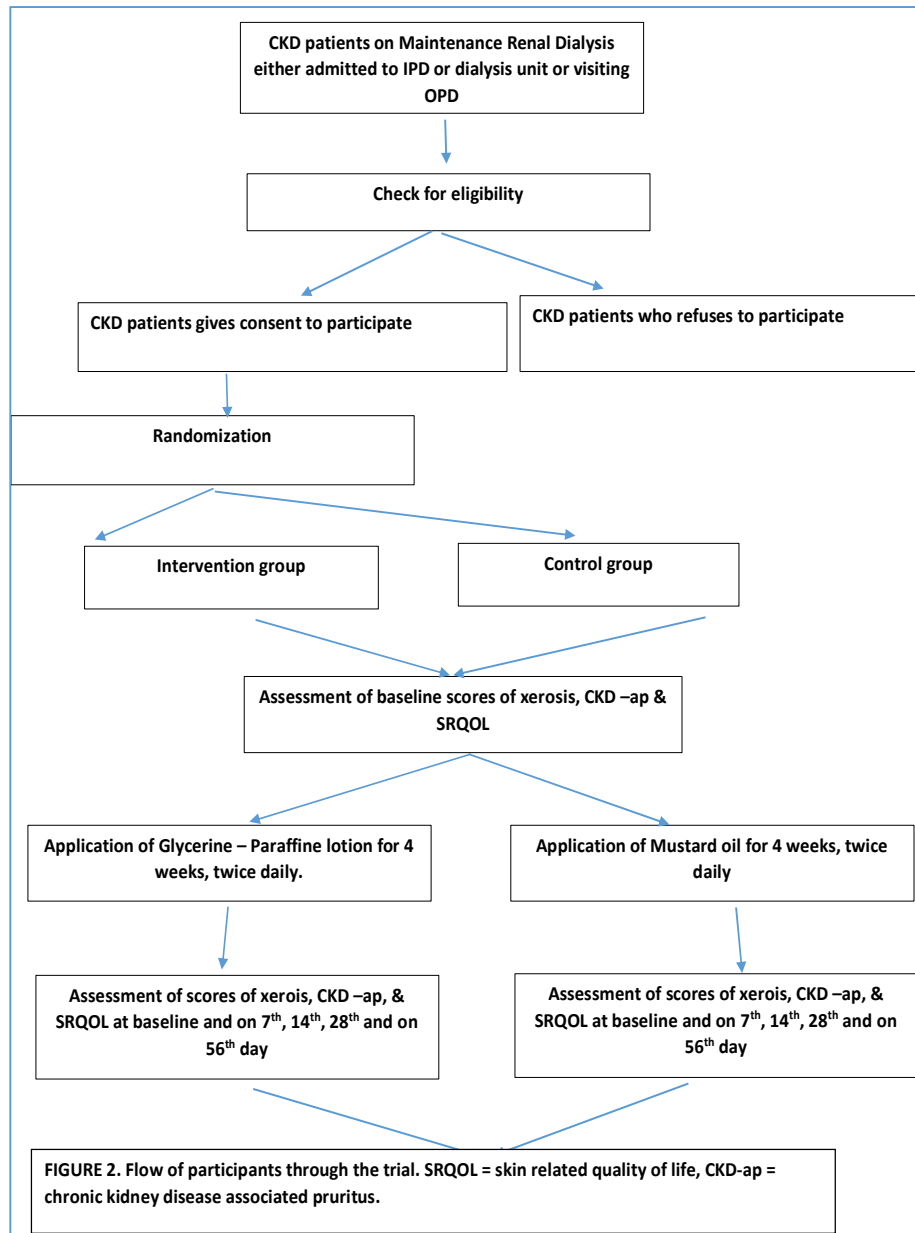


Fig. 1. Flow chart

Data management: Once data collection has been completed & checked, the process of data entry and data cleaning will be done within 7 days. All verbal & numeric data collected using questionnaire or observation will be entered in a computerised master chart as numeric data code. Qualitative variables will be coded yes -1, No- 0.

Statistical methods: Descriptive analysis (Mean, Mean percentage & Standard deviation)

will be used for quantitative variables, frequency & proportion for categorical variables. Appropriate diagram like bar & pie diagram will be used for representation of data. Moreover, between group comparison, chi square test or Fisher exact test or proportion test, whichever will be applicable will be applied and p value less than 0.05 will be considered as significant. Between group comparison of quantitative variables, t -test, ANOVA which ever will be applicable will be applied.

SPSS version 22.0 software and Microsoft Excel 13.0. will be used for all analysis.

Data monitoring: Data collection is the whole sole responsibility of investigator and data monitoring will be done by guide & co- guide Dr. Mrs. Meenakshi Yeola & Mrs. Ruchira Ankar.

Auditing: no external auditing committee is appointed, the investigators only will audit the trial time to time for progress.

5. RESULTS

In line with experimental evidences, we assume that there could be a positive response with glycerine paraffin combination to mitigate the manifestations of CKD-ap & uremic xerosis and it may also improve the skin related quality of life (SRQOL).

6. DISCUSSION

This is a randomized, single blind, controlled clinical trial with primary objective of comparing the efficacy of Glycerine- Paraffin combination with Mustard oil among CKD patients having CKD-ap & uremic xerosis.

150 CKD patients with mild to moderate xerosis will be randomly allocated to control & experimental group. Experimental group will apply glycerine- Paraffin combination & mustard oil to control group twice a day for a month.

Glycerol 10% and Paraffin 15% combination is found to be effective in managing uremic xerosis [13]. Mustard oil is chosen as a comparator as it is commonly used home remedy by people in Indian sub-continent for dry skin [14,15]. Management of uremic xerosis can be done effectively with appropriate emollient use [16]. Glycerol keeps the skin hydrated and supple whereas Paraffin protect the skin from chemical irritant by improving its barrier function [17,18]. Studies on various aspects of chronic renal diseases were reported [19-23]. Studies from Global Injury were reviewed [24,25].

In view of evidences generated by various old studies we assume that glycerine – paraffin combination will minimize the uremic xerosis and relieve pruritus thereby improve the overall skin related quality of life among CKD patients [26-28].

7. CONCLUSION

In conclusion the study will help the CKD patients to choose better line of treatment to manage uremic xerosis & CKD-ap. It will help the health care professionals to develop & implement a universal skin care protocol for patients of CKD in hospital & at dialysis centres.

CONSENT AND ETHICAL APPROVAL

The synopsis of the study had been reviewed and approved by the Institutional Ethics Committee of Dutta Meghe Institute of Medical sciences on 10/10/20 and registered in Control Trial Registry of India on 1/12/20. Any amendment of study protocol & consent form will be valid only after recommendations of institutional ethics committee.

The principal investigator will give the complete information about study, its purpose to study participant and will take the informed and written consent. Random codes & participant's initials will be used for collection of data. Any personal information including identification code and their name will be kept confidential and would not be noted down in the case record form.

The details of datasets used or analysed after study completion will be available from the corresponding author under reasonable requests. The findings of the study and its implication will be disseminated via publication.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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