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Assessment of the Routine Functional Activities in the Comparative Siddha Medical Treatment for Symptomatic Knee Osteoarthritis in Jaffna District, Sri Lanka

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Authors' contributions

This work was carried out in collaboration between all authors. Author SV designed the study, performed the statistical analysis, wrote the protocol and first draft of the manuscript. Authors IT and SSR managed the analyses of the study. Author SSR managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Knee Osteoarthritis (KOA) is a most common form of the rheumatic disease and relatively the prevalence is higher in Asians than in Western populations. KOA is one of the five leading causes of disability among elderly men and women. The scope of this study was to assess the routine functional activities by WOMAC score in the Siddha medical treatment for symptomatic KOA in Jaffna District, Sri Lanka.
Study Design: This was an open, randomized, parallel group of comparative clinical trial.
Place and Duration of Study: This study was carried out in selected Government Ayurveda Hospitals in Jaffna District, Sri Lanka between January 2013 and August 2014.

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Methodology: This clinical trial was conducted based on American College of Rheumatology (ACR) classification, 837 KOA subjects were screened and 250 KOA subjects of both genders, aged ≥40 years were randomly selected at Out Patients Department of Ayurveda Hospitals. Selected subjects were alternatively divided into two groups as group A and group B. The group A were received 'Medicine A' {2 capsules of 1 g *Amukkirai Chooranam* with *Thalangai ennai* (external application)} while group B was received 'Medicine B' {2 capsules of 1g *Vellarugu Chooranam* with *Thalangai ennai*} twice daily, up to 40 days. The modified Indian version of Western Ontario and McMaster Universities Arthritis Index (WOMAC) score was the primary outcome variable used to assess the self-reported pain, stiffness and physical functions based on the life style activities. The collected data were analyzed by the SPSS version 17.

Results: There were 177 (70.8%) female and 73 (29.2%) male with a mean age of 57.02 (SD±8.78) years. At the end of treatment, for group A, the mean total WOMAC score was reduced from 156.03±53.83 to 78.68±37.11 while for group B, that score was reduced from 165.29±57.19 to 83.79±41.08. Although there was a significant reduction in pain, stiffness, physical function and total score (P=0.000) for WOMAC index during routine functional activities at end of the treatment in each group, there was no significant differences (P>0.05) observed between both groups.

Conclusion: The Present study also strengthens the contemporary area of comparative effectiveness of selected siddha medication (both *Amukkirai Chooranam* and *Vellarugu Chooranam* together with *Thalangai ennai*) in routine functional activities in the treatment of symptomatic KOA treatment over 40 days of therapy.

Keywords: Assessment; factors; knee osteoarthritis; life style; Siddha Medicine; symptomatic; treatment; WOMAC score.

1. INTRODUCTION

Knee Osteoarthritis (KOA) is a most common form of rheumatic disease and a progressive degenerative joint disorder characterized by gradual loss of cartilage [1]. KOA results from mechanical and idiopathic factors that alter the balance (irreversible pathological changes) between degradation and synthesis of articular cartilage and sub chondral bone and characterized by slowly developing joint pain, short-lived morning stiffness, reduced function, instability, deformity, joint swelling, crepitus and activity limitations [2,3]. Disease progression is usually slow but can ultimately lead to joint failure with pain and disability [4].

KOA is one of the five leading causes of disability among elderly men and women and the risk for disability from KOA is as great as that from cardiovascular diseases [5]. A previous study mentioned that KOA is likely to become the fourth most common cause of disability in women and the eighth most common cause in men [6]. The aetiology of KOA is not entirely clear, yet its incidence increases with advancing age [7,8] and in women. Risk factors for developing KOA are well known and include older age, gender, obesity, previous injury or trauma and genetic factors, etc. [3,6]. The findings of the risk factors associated with KOA study in Jaffna District indicated that there was a significant association between age, sex and BMI with KOA. [9]. Two systems of Medicine namely Allopathic, and Indigenous are mainly practised in Sri Lanka. In all the three indigenous systems (Ayurveda, Siddha and Unani Medicine) in Sri Lanka, plants play a major role and constitute the backbone of the system. Siddha Medicine is one of the Traditional Medicine and popular among the Tamil speaking people of Northern and Eastern Provinces of Sri Lanka [10]. In general, Siddha medications are mainly of herbal origin. In Siddha system, equal importance has been given to internal as well as external medicine because Siddha Medicine advocates 32 types of internal and 32 types of external medicine with their shelf life [11].

The researcher observed during her practice and Medical Officer period, that *Amukkirai* and *Vellarugu chooranam* (Single herbal powder medicine) as internal medicine and *Thalangai ennai* (Medicated oil) as external application were very effective in the treatment of musculoskeletal conditions such as osteoarthritis, back pain, joint pain etc. As the scientific approach of efficacy is not tested so far, this study was planned to assess the lifestyle activities by WOMAC Index Score in these two combinations {*Amukkirai Chooranam* (A.C) with *Thalangai ennai* and *Vellarugu Chooranam* (V.C) with *Thalangai ennai*} of siddha medicines for the treatment of symptomatic KOA.

2. METHODOLOGY

2.1 Study Design

This was an open, randomized, parallel group of comparative clinical trial four interventions and two follow-up arms.

2.2 Study Area

This study was carried out in selected Ayurveda Hospitals in Jaffna District which is one of the 25 Districts of Sri Lanka and is located in the Northern part of Sri Lanka. Jaffna District is divided into four major divisions and for the administrative purposes, these major zones are further divided in to 15 Divisional Secretariats (DS) divisions or Assistant Government Agent (AGA) divisions (Appendix 1).

The health services in Indigenous Medical systems are carried out through the Government Ayurveda Hospital, District Ayurveda Hospital, Rural Ayurveda Hospital, Central Ayurveda Dispensaries and Free Siddha Ayurveda Dispensaries. At present, fifty-three (53) Ayurveda Institutions are functioning under the 13 DS divisions. The thirty-two hospitals (60%) were sampled from thirteen DS divisions for this research study. The hospitals/ Dispensaries were selected from each DS division as random depending upon their average number of patients attending the clinic per day. Suitable trial KOA subjects were selected in twenty-five (78.12%) out of thirty-two Ayurveda Hospitals/ Dispensaries in Jaffna District and rest of the seven Hospitals did not satisfy the inclusion criteria. Facilities at the site were adequate to support the study.

2.3 Study Unit

The study unit consists of two hundred and fifty KOA subjects, who attended Out Patients Department (OPD) of twenty-five Ayurveda Hospitals / Dispensaries in Jaffna district for the treatment.

2.4 Study Duration

This trial was carried out from January 2013 to August 2014 (20 months).

2.5 Study Population

2.5.1 Inclusion criteria

Subjects of either gender ≥ 40 years age; pain visual analogue score (VAS) ≥ 4cms in one or both knees while performing a weight bearing activity (e.g. walking, standing, climbing staircase); diagnosis of KOA based on history, clinical examination findings and classical radiological findings, and fulfilling the American College of Rheumatology(ACR) classification criteria [12] except that the lower age limit was reduced to 40 years; and radiographic evidence of OA was based on the ranking score of the Kellgren-Lawrence radiographic system [13].The KOA either grade I or grade II or grade III severity was considered as a condition of inclusion.

2.5.2 Exclusion criteria

Subjects who have non-degenerative joint diseases or other joint diseases such as rheumatoid arthritis, psoriatic arthritis, gonococcal arthritis and haemoarthritis; subjects with severe disabling arthritis and/or the patient are bedridden; those that had history of intra-articular knee injection within the month preceding the study; those with evidence of severe unstable renal, hepatic, diabetic, haemopoietic, cancer, hypertensive, cardiac disorder and mentally affected as revealed by history and / or investigation; subject taking antipyretics, analgesics, tranquilizers, hypnotics, alcohol, or any other drug which would interfere with pain perception and need for other drug therapy for osteoarthritis; subjects with acute illness; women who are pregnant, lactating, having child bearing potential and not following adequate contraceptive measures.

2.5.3 Sample size and screening

Sample size was determined by the retrospective data collected from the records of Ayurveda Hospitals and / Dispensaries in Jaffna District from March 2009 to June 2010, 46% (363 / 783) KOA patients who took treatment (Source: Medical records from Ayurveda Hospitals/ Dispensaries in Jaffna, 2010). The sample size was calculated by the sample size calculator method [14] and two hundred and fifty (250) KOA subjects were included in this trial.

2.5.4 Screening

All selected KOA subjects were screened for hypertension and diabetes mellitus at the onset of the study.

2.6 Selected Medication

2.6.1 Internal medicine (medicated capsules)

The standardized trial medicines such as *Vellarugu Chooranam* (V.C) and *Amukkirai Chooranam* (A.C) (Single herbal formulations) were filled separately in to empty gelatin capsules (which were purchased from Arkem Pharmaceuticals, Prince of Walse Avenue, Colombo-14, Sri Lanka) using a manual capsule filling machine {VITRO-CAPSULE FILING MACHINE (100 holes) / Mumbai}. All personal and environmental protective measures were maintained. Each capsule ('0' size) contained 500 mg of trial plant material.

2.6.2 External application (medicated oil)

Thalangai Ennai (Poly herbomineral formulation) was purchased from Everest *Marunthakam, Usan, Mirusuvil*, Sri Lanka and then it was poured into 100ml plastic containers and labeled.

2.6.3 Storage and coded combinations

Filled capsules of each trial medicine were packed and labeled separately. Then these were kept in the fridge below 21°C (70°F) for further trial study (http://www.spicesinc.com/). Two combinations of herbal medicines such as A.C with T.E and V.C with T.E were coded as 'Medicine A' and 'Medicine B'.

2.7 Ethical Approval

Prior to the commencement of study, certificate of ethical clearance for the clinical trial was obtained from the Ethical Review Committee of the Faculty of Medicine, University of Jaffna on 2012. The subjects were assured that strict confidence would be maintained in respect of this study. Online trial registration (Reg. no: SLCTR/ 2012/ 009) was done at Sri Lanka Clinical Trials Registry (SLCTR) of Sri Lanka Medical Association, Colombo, Sri Lanka.

Prior to data collection, permission and written approval were obtained from the Commissioner of Ayurveda, Provincial Commissioner of Indigenous Medicine, Regional Assistant Commissioner and for conduct this study at Ayurveda Hospitals/ Dispensaries in Jaffna District.

2.7.1 Adverse events monitoring committee

Adverse Events Monitoring Committee for the clinical trial was formed by the researcher. Adverse events were monitored by Adverse Events Monitoring Committee which consist one Consultant Physician from Teaching Hospital, Jaffna and two Siddha Physicians (M.O.I.Cs.) from Ayurveda Hospitals in Jaffna.

2.8 Data Collection

2.8.1 Recruitment procedures and consenting

2.8.1.1 Selection of the subjects

In all selected Ayurveda hospitals the KOA subjects were those who came to the out patients departments (OPD) on their first visit. The dates of this study selection were according to the convenience of the researcher. The DS division and the Hospital were selected by toss method for the first visit. The researcher visited the Ayurveda hospitals which are under one DS division during the first six weeks. Subsequently, these DS divisions were visited by the researcher in the same manner. The selection was made for all suitable KOA subjects who came to the OPD on those days. There was no bias introduced by the researcher. Contacts were made with the subjects via telephone.

2.8.1.2 Sampling techniques and randomization process

Trial medicine and the group were also selected by toss method for first issue. Eligible KOA subjects were enrolled on simple random method. Subjects were assigned for treatment arm in a 1:1 ratio in any of the two combinations (A and B) of the treatment groups alternatively.

2.9 Study Instrument

2.9.1 Questionnaire

WOMAC {Western Ontario and McMaster University's OA Index} Assessment which is a tridimensional self-administrated questionnaire for assessing health status and health outcome (lifestyle activities) in KOA and it has been accepted globally [15]. But patients of different educational backgrounds, socio-economic and cultural diversities may overrate or underrate their functional ability status. Therefore, it was validated for local use from modified version of WOMAC (Version LK3) questionnaire for Indian use [16]. The WOMAC index (Appendix 2) was conducted at each interventions and follow-up period. This modified WOMAC index scoring system (Likert scale) was calculated for each of

the three domains (pain, stiffness, physical function) and a WOMAC total score was computed as the un-weighted mean of all 30 items. It consists of 30 questions (13 related to pain and 4 related to stiffness and 13 related to physical function). These questions were assessed subjective (face to face interview) only and categorized as none, mild, moderate, severe, and extreme (1-5 score). The score of all the answers was summed (30 questions with a maximum score of 150) up.

2.9.2 Informed consent form

Information sheet with a certificate of written consent form (bilingual) were prepared for the clinical trial subjects consent. Detail of study was explained to the subject and their written consent was obtained from each subject before the commencement of data collection.

2.10 Pilot Study

Prior to the commencement of main study, the pilot study was carried out on 16 knee osteoarthritis subjects who attended Ayurveda Hospitals in Jaffna District and tested the adequacy of the research instrument questionnaire. After the pilot study analysis, minor changes have been done in the questionnaire. Subjects selected for the pilot study were not included in the main study.

2.11 Study Procedure

2.11.1 Visits to Ayurveda Hospitals (Mode of collection)

All subjects diagnosed as KOA were examined by researcher on their first visit to the OPD. All relevant information was collected by interrogation and observation. In addition diagnostic cards or earlier medical records were looked into get further information.

After identifying the eligible subjects, questionnaire was administered. Diagnosis of KOA of the selected subjects and progression of their condition was assessed by the orthopedic surgeon (Consultant)/ Teaching Hospital, Jaffna.

2.11.2 Treatment

Selected subjects were assigned to treatment “Group A” or “Group B” alternatively. The recommended daily dose of experimental medicine was 2 g (500 mg trial plant material / capsule) and local applications of oil {5-10ml} (“Medicine A” or “Medicine B”). The prescribed dose was two capsules (A.C / V.C) to be taken with lukewarm water after meals and oil (T.E) application twice a day for 40 days.

2.11.3 Intervention and clinical evaluation

There are seven interventions. End point evaluation was made at baseline, at 10^{th}, 20^{th}, 30^{th}, 40^{th} days of intervention and then follow-up measures after completion of prescribed dosage of end of first and second month. In every intervention, the WOMEX Index was assessed.

2.11.4 Adverse events

Patients were specifically questioned as per a predetermined list of common symptoms (anorexia, nausea, vomiting, diarrhoea, constipation, dysuria, skin rash, giddiness, oral mucous ulcers, dyspepsia, abdominal discomfort, and pain) based on experiences in clinical practice. All adverse events reported by the subjects and/ or observed by the researcher were recorded with information about date of onset, duration and degree of severity during the intervention and follow-up studies. The appropriate action was taken by the researcher.

2.12 Statistical Analysis

The collected data were processed and analyzed by the standard statistical software program SPSS (Statistical Package for the Social Sciences) version 17. The probability level was set as $P<0.05$. All primary endpoints can be regarded as continuous random variables and therefore similar analysis methods were undertaken. Within-group analyses were conducted using the paired student t-test to assess change in the outcome variables between baseline and interventions and follow-ups. Between-groups analyses were conducted using the Independent samples t-test.

3. RESULTS AND DISCUSSION

3.1 Characteristic of the Subjects and Participant Flow

During this study, 837 subjects with KOA were screened by the researcher. Among these 837 subjects, 362 (43.25%) were eligible and met the inclusion criteria. Of these 362 subjects, 112 (30.94%) subjects declined to participate and they were considered as non-respondents. The remaining 250 (69.06%) subjects were divided

into two treatment groups as A and B alternatively and leading to a total of 125 subjects of the each group participating in the trial (Fig. 1). The most common reason for exclusion was acute traumatic condition in 43 (9.05%) subjects, and associated with other diseases in 432 (90.95%) subjects.

Course of treatment and period of follow-up measures were completed by 243 (97.2%), and 220 (88%) subjects respectively. Totally 30 (12%) of the selected KOA subjects were withdrew from the study at different stages. Among these subjects, 16 (6.4%) and 14 (5.6%) of KOA subjects were withdrew from the treatment group A and B respectively. Low number of subjects 30 (12%) withdrew from the present study and similar number of patients have been reported to withdrew from KOA related RCTs in previous studies [17,18].

FLOW CHART

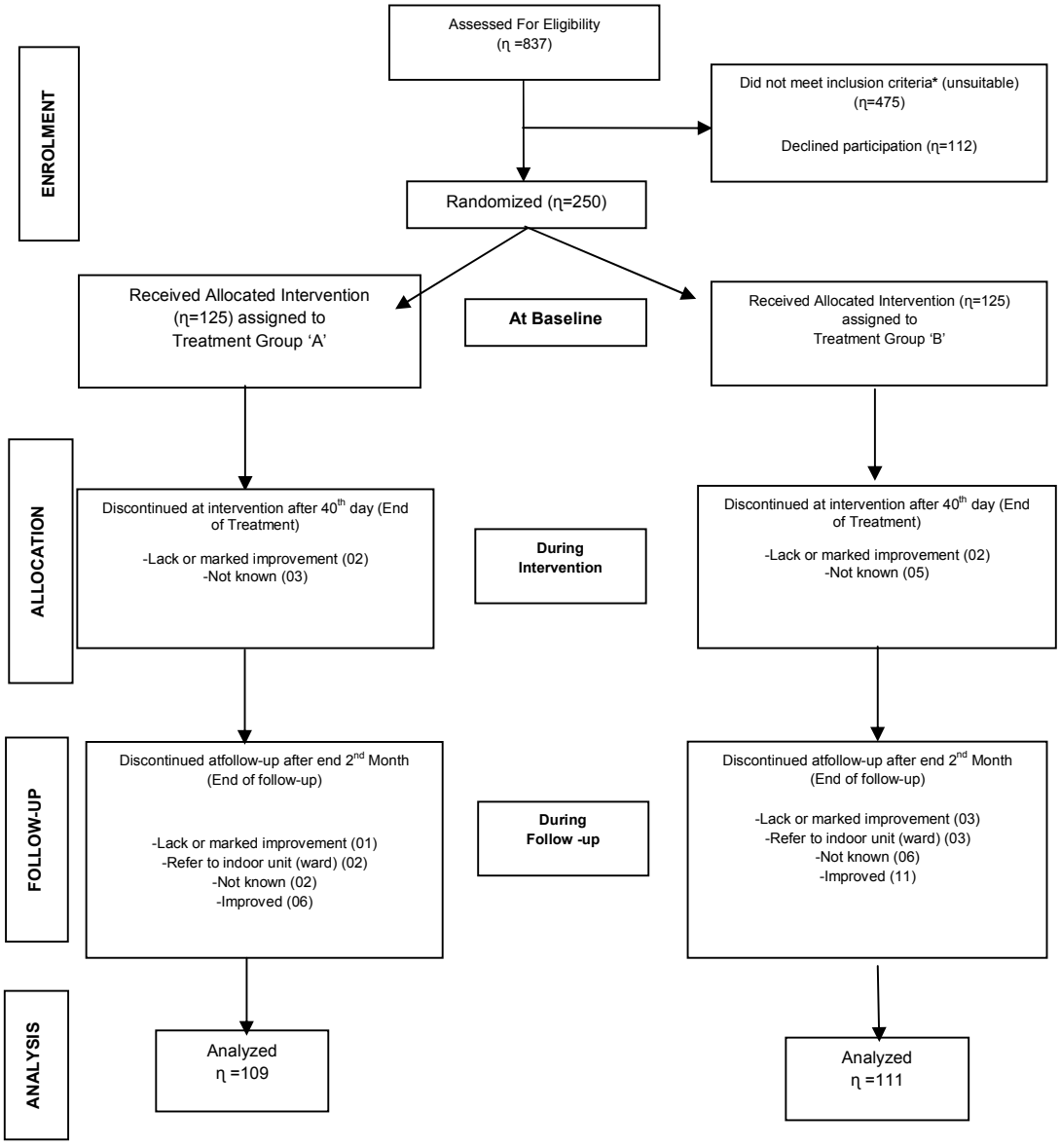

Fig. 1. Flow chart indicating subjects' enrolment; group allocation and analysis according to CONSORT guidelines

3.2 Distribution of Demographic Characteristics of Study Population at Baseline

The mean age of the subjects in group A and group B were 56.95 (SD±8.79) and 57.10 (SD±8.81) years respectively. Majority of subjects in group A {29 (23.2%)} and group B {32 (25.6%)} were between 55-59 years of age. The majority of subjects in group A {86 (66.8%)} and group B {91 (72.8%)} were female.

Table 1 shown, there was no significant differences (P>0.05) were found in demographic characteristics e.g., age, religion, civil status, level of education and occupation of the KOA subjects in between two recruitment groups (A and B) in both sex at baseline.

3.3 Distribution of Characteristics of KOA

The characteristics of the KOA in the two recruitment groups in both genders are showed in Table 2.

No significant differences were found in characteristics such as duration of the KOA and affected side between two groups. There was no remarkable difference in affected right and left knees between two groups at baseline.

Table 1. Demographic characteristics of the study population at baseline

Characteristics	Group 'A' (η=125)		Group 'B' (η=125)		P-value
Gender	**η**	**%**	**η**	**%**	0.49
Female	86	66.8	91	72.8	
Male	39	31.2	34	27.2	
Age (years):	**η**	**%**	**η**	**%**	**0.70**
40-44	13	10.4	10	08.0	
45-49	17	13.6	19	15.2	
50-54	19	15.2	14	11.2	
55-59	29	23.2	32	25.6	
60-64	20	16.0	25	20.0	
65-69	17	13.6	14	11.2	
70-74	05	04.0	07	05.6	
≥ 75	05	04.0	04	03.2	
Mean age:	**(Mean ± SD)**		**(Mean ± SD)**		**0.89**
Total	56.95±8.79		57.10±8.81		
Female	55.37±8.53		55.67±8.55		
Male	60.44±8.44		60.91±8.47		
Religion:	**η**	**%**	**η**	**%**	**0.59**
Hindu	83	66.4	87	69.6	
Christian	42	33.6	38	30.4	
Civil status:	**η**	**%**	**η**	**%**	**0.56**
Married	95	76.0	95	76.0	
Single	30	24.0	30	24.0	
Level of education:	**η**	**%**	**η**	**%**	**0.44**
Illiterate	01	00.4	00	00.0	
Gr. 1- 5	19	15.2	23	18.4	
Gr. 6 -10	33	26.4	39	31.2	
GCE O/L – A/L	68	55.4	58	46.4	
Higher education	04	03.2	05	04.0	
Occupation:	**η**	**%**	**η**	**%**	**0.82**
Professional	01	00.8	03	02.4	
Non professional	07	05.4	03	02.4	
Skilled worker	09	07.2	07	05.6	
Unskilled worker	20	16.0	20	16.0	
House wives	73	58.4	78	62.4	
Retired person	07	05.4	09	07.2	
Unemployed	08	06.4	05	04.0	

*η: Frequency; %: Percentage; *P<0.05; SD- Std. deviation*

In addition according to the inclusion criteria of radiographic evidence, number of 'eligible knees' for each group were calculated. As per the inclusion/exclusion criteria, only those with grade I, grade II and grade III KOA were accepted into this study. In radiological evidence, majority of the subjects (>57%) were affected by grade II level in both recruitment groups. There was no significant difference in radiological evidence of affected right and left knees between two groups at baseline.

3.4 Distribution of WOMAC Index Characteristics of Study Population

The WOMAC index characteristics of the KOA in the two recruitment groups are shown in Table 3.

The WOMAC analysis included four indices: pain, physical function, stiffness, and a total score. Data were tested for normality at baseline. Equal variances were assumed for function and total score and equal variances not assumed for pain and stiffness. Results indicated that score of each component for group A and group B were all normally distributed. There were no significant differences between the two groups on the pain (p=0.24), stiffness (p=0.25), physical function (p=0.17) and total score (p= 0.19) at baseline.

3.5 Assessment of Lifestyle Activities by WOMAC Index Score during Clinical Trial

3.5.1 Between group analyses

The improvement status of WOMAC index of the both groups was assessed by two indices at 4th intervention (End of the treatment) and 2nd follow-up period (Table 4).

When the statistical analysis between groups was performed, the WOMAC index that assessed pain, function, stiffness and total score during daily activities did not differ significantly between both groups during the end of the treatment and follow-up period.

Table 2. Characteristics of the KOA at baseline

KOA characters	Group 'A' (η=125)		Group 'B' (η=125)		P
	η	%	η	%	
Duration of KOA					
< 1 year	66	52.8	65	52.0	
1-5 years	53	42.4	55	44.0	0.67
> 5 years	06	4.8	05	4.0	
Affected side					
Right	45	36.0	41	32.8	
Left	33	26.4	28	22.4	0.34
Both	47	37.6	56	44.8	
Average eligible knees	1.38		1.45		

*η: Frequency; %: Percentage; *P<0.05*

Table 3. Independent samples t-test for the WOMAC Index characteristics of the KOA at baseline

#WOMAC Index	Groups	η	Mean ± SD	t	Sig.
1. Pain	Group A	125	67.80±23.80	-1.19	0.24
	Group B	125	71.50±24.54		
2. Stiffness	Group A	125	17.70±08.96	-1.16	0.25
	Group B	125	19.10±09.74		
3. Physical function	Group A	125	70.50±23.61	-1.38	0.17
	Group B	125	74.74±25.04		
4. Total score	Group A	125	156.03±53.83	-1.32	0.19
	Group B	125	165.30±57.19		

*#WOMAC index consists of 30 questions, assessed on 1-5 likert scale, analyzed in 3 subscales as the average score for 13 questions on pain, 4 questions on stiffness and 13 questions on physical function. The total score is calculated as the mean score for a 30 questions; η: Frequency; *P<0.05*

Table 4. Changes in WOMAC index for Pain, Physical function, and Stiffness between groups at end of the treatment and end of the follow-up

WOMAC Index	Time Period	ɲ	Treatment Groups	Mean ± SD	t-	Sig.
Pain	Base	125	Group A	67.80±23.80	-1.19	0.24
		125	Group B	71.50±24.54		
	4th Int.	120	Group A	27.10±14.74	-1.14	0.26
		123	Group B	29.40±16.96		
	2nd Fwp.	109	Group A	22.70±12.12	-0.06	0.96
		111	Group B	22.80±10.85		
Physical function	Base	125	Group A	70.50±23.61	-1.38	0.17
		125	Group B	74.74±25.04		
	4th Int.	120	Group A	45.12±21.10	-0.96	0.34
		123	Group B	47.78±21.97		
	2nd Fwp.	109	Group A	26.14±13.42	-0.40	0.69
		111	Group B	26.84±12.73		
Stiffness	Base	125	Group A	17.70±08.96	-1.16	0.25
		125	Group B	19.10±09.74		
	4th Int.	120	Group A	06.08±03.17	-1.18	0.24
		123	Group B	06.59±03.66		
	2nd Fwp.	109	Group A	05.83±02.80	0.10	0.92
		111	Group B	05.80±02.26		
	Base	125	Group A	156.03±53.8	-1.32	0.19
		125	Group B	165.30±57.2		
Total score	4th Int.	120	Group A	78.68±37.10	-1.02	0.31
		123	Group V	83.79±41.10		
	2nd Fwp.	109	Group A	54.64±27.50	-0.21	0.83
		111	Group V	55.40±24.90		

**P < 0.05; ɳ- Number of Subjects; Int.-Intervention; Fwp. - Follow-up*

3.5.2 Within-group analyses

The mean changes for each group (within-group analysis) in WOMAC index that assessed pain, stiffness, function and total score at the end of 4th intervention and 2nd follow-up decreased significantly when compared to their own baseline values in order to investigate the effectiveness of the treatment based on the change in the WOMAC Index during course of trial. The results are shown in Table 5.

Table 5. Mean changes in WOMAC index for Pain, Physical function, Stiffness, and Total score from baseline to end of the treatment and end of the follow-up

WOMAC Index	Time period	Group A			Group B		
		Mean differences (M ± SD)	t	ɲ	Mean differences (M ± SD)	t	ɲ
Pain	Base vs. 4th Int.	41.23±16.15	27.97**	120	42.04±16.41	28.41**	123
	Base vs. 2nd Fwp.	46.16±16.51	29.18**	109	47.04±16.92	29.28**	111
Physical function	Base vs. 4th Int.	25.72±11.44	24.72**	120	45.34±16.91	29.73**	123
	Base vs. 2nd Fwp.	45.27±15.97	29.60**	109	46.18±16.81	28.94**	111
Stiffness	Base vs. 4th Int.	11.58±07.76	16.34**	120	12.41±08.09	17.01**	123
	Base vs. 2nd Fwp.	11.85±07.93	15.60**	109	13.06±08.21	16.77**	111
Total score	Base vs. 4th Int.	78.28±29.14	29.42**	120	81.43±33.06	27.32**	123
	Base vs. 2nd Fwp.	103.3±35.99	29.96**	109	106.3±38.92	28.77**	111

***P < 0.000; ɲ - Number of subjects; Int.-Intervention; Fwp. - Follow-up*

For group A, the analysis indicated that KOA subjects had a highly significant reduction in pain, stiffness, physical function and total score for WOMAC index between the baseline and 4th intervention and 2nd follow-up period (p=0.000). The mean total score had decreased from 156.03 ± 53.83 to 78.68 ± 37.11 at the end of treatment and to 54.64 ±27.52 at the end of follow-up.

Similar findings were seen in the group B. Subjects showed a positive response in the relief of pain, stiffness, physical function, and total score for WOMAC index between the baseline and 4th intervention and 2nd follow-up period (p=0.000). The mean total score had decreased from 165.29 ± 57.19 to 83.79 ± 41.08 at the end of treatment and to 55.40 ± 24.99 at the end of follow-up.

At the end of follow-up, the percentages of improvement in WOMAC index that assessed pain, stiffness, physical activities and total score were higher than 60% in both groups.

The primary outcome variable, the WOMAC index, is an OA disease-specific instrument, so it more accurately reflects the efficacy of a therapy for OA patients [19]. In this present study results were comparable with the numerous non pharmacological and pharmacological therapy related studies. Although, the studies design, number of subjects, inclusion criteria, age limit and assessment methods were different from the present study.

Singh et al., conducted quasi experimental study (n=30) of *Commiphora Mukkul* (500mg) effectiveness in the treatment of KOA and found that there was a significant difference in the scores of the primary and secondary (WOMAC) outcome measures (P<0.0001) at the 2 month and follow-up [20]. A previous randomized, 8 weeks controlled trial (n=68) of Swedish massage therapy for KOA demonstrated that there was significant improvements (P<0.001) in the mean (SD) WOMAC global scores for pain, stiffness, and physical function [21]. Chopra et al., have reported that the active group showed significant reduction in WOMAC index (P<0.01) superior than placebo group [22]. Chopra et al., have stated that, active herbal formulation group showed significant reduction in rates for WOMAC (p=0.04) for pain, stiffness and difficulty compared with placebo in the symptomatic treatment of KOA [23] and further Chopra et al., demonstrated that there was no significant differences in primary efficacy analysis (P<0.05) for WOMAC questionnaire (knee function) in standardized treatment group [24]. Another study has stated that the within-group analysis (Chinese Herbal Medicine and placebo) showed that KOA symptoms had significantly improved at the end of the herbal treatment as measured by a reduced WOMAC scores and the placebo was also found to reduce the WOMAC scores (but not the stiffness score) over 12 weeks in Australia. However, there was no statistical significance between the two groups in terms of WOMAC scores for pain, stiffness physical activity and total score. Therefore, the clinical significance of their study is actually not clear. However, there were only 47 participants recruited into the study and sample sizes were unequal and trial over in 12 weeks, with a one month follow-up [25]. Mehdi has also stated that significant improvements in WOMAC score for the experimental group (p≤0.001) when compared with control group (p=0.878) in relation to pain, stiffness and functional activities in the study evaluated the effectiveness of combined manual physical therapy and exercise in individuals with KOA [26].

Recently, many RCTs of KOA have shown that the herbal medicines reduced pain, disability, and improved mobility with a low incidence of adverse effects [18,20,24,27,28,29,30,31]. In present study results were supported to these findings by showing that the both combination of herbal medicines are effective and safety in the treatment of KOA.

Many randomized double blind, parallel efficacy clinical trials of KOA also have shown that the pharmacological therapies (NSAID) had significant final differences on the WOMAC total index and pain, function, and stiffness subscales with placebo [32,33,34,35,36,37]. Many pharmacological related randomized clinical trials have shown that the oral medicines like glucosamine sulfate, celecoxib, chondroitins, and doxycycline did not produce significant improvement in sign and symptoms of KOA than placebo [35,38,39,40,41,42]. Over all above said studies results were not comparable to this present study because, study design, study area, type of treatment, selection criteria, and study population, etc. were different from the present study.

4. CONCLUSION

In the present study findings revealed that both herbal medicines together with T.E have

statistically significant reduction in pain, stiffness, physical function and total score (*P*=0.000) for WOMAC index during routine functional activities at end of the treatment and end of the follow-up in each group, there were no significant differences (*P*>0.05) observed between the both groups. The within-group analysis showed that KOA symptoms had significantly improved at the end of the both herbal treatment. These herbal medicines did not show any adverse effects or side effects during the treatment and follow-up periods. The Present study also strengthens the contemporary area of comparative effectiveness of selected siddha medication (both *Amukkirai Chooranam* and *Vellarugu Chooranam* together with *Thalangai ennai*) in routine functional activities in the treatment of symptomatic KOA treatment over 40 days of therapy.

5. LIMITATION OF THE STUDY

In this present study control drug was excluded because the non availability of a standard drug for Osteoarthritis treatment in Siddha Medicine to do the control trial. At the same time, placebo was not used for comparing the efficacy in this study because according to ethical guidelines, does not allow the subjects suffering from pain and discomfort.

6. RECOMMENDATION

The modified Indian (Asian) version of WOMAC will be changed to Sri Lankan population and used in the present trial would need to be evaluated in the similar clinical trial.

CONSENT

As per international standard or university standard, written informed consent was obtained from KOA subjects and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard written ethical permission has been obtained from Ethical Review Committee of the Faculty of Medicine, University of Jaffna and Sri Lanka Clinical Trials Registry of Sri Lanka Medical Association, Colombo, Sri Lanka and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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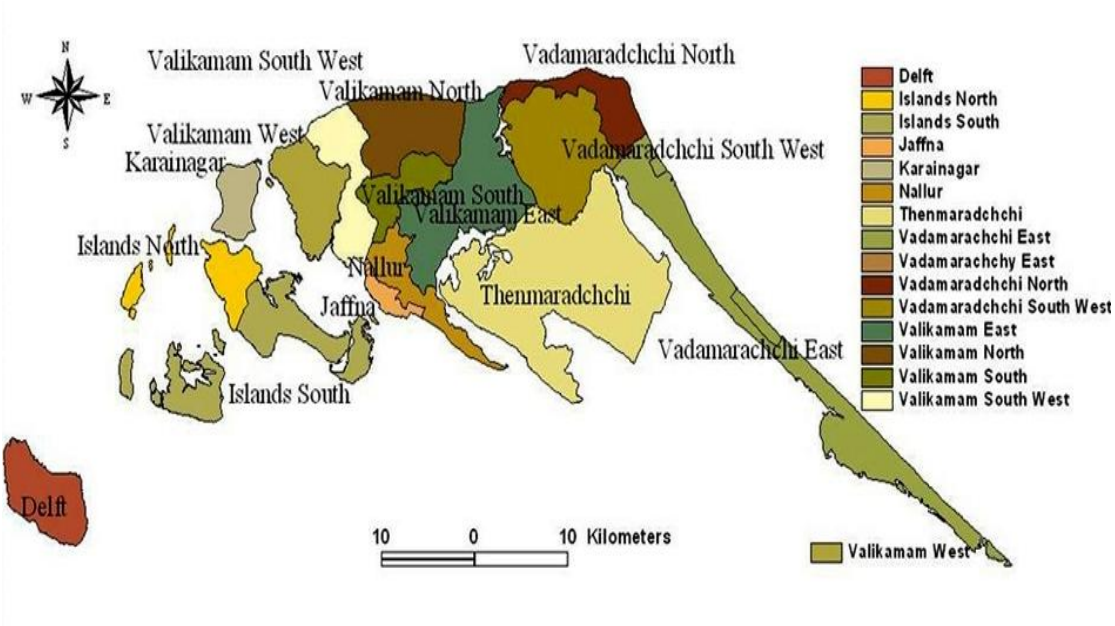
APPENDIX



Appendix 1. Areas under the DS divisions in Jaffna District

Serial No: …….

Date: ……

DATA COMPILATION FORM

MONITORING THE SYMPTOMS OF THE KOA {WOMAC INDEX}

1. Think about the pain you felt and the difficulty you had in doing the following daily physical activities during the last 48 hours. How much pain and difficulty have you had….
{Score: None 1; Mild 2; Moderate 3; Severe 4; Extreme 5}

No	Daily Physical activities	Pain		Difficulty in function	
		Right	Left	Right	Left
1.1	When walking on a flat surface?				
1.2	When going up the stairs?				
1.3	When going down the stairs?				
1.4	While sitting?				
1.5	While standing?				
1.6	While lying down?				
1.7	When getting up from the sitting position?				
1.8	When bending to the floor?				
1.9	While lying in bed?				
1.10	When getting out of bed?				
1.11	When getting on the toilet?				
1.12	When getting off the toilet?				
1.13	While doing routine work?				

2. Think about the stiffness (not pain) you felt during the last 48 hours. How much severe has your stiffness been....?
{Score: None 1; Mild 2; Moderate 3; Severe 4; Extreme 5}

No	Activities	Stiffness	
		Right	Left
02.2.1	After you first woke up in the morning?		
02.2.2	After sitting?		
02.2.3	After lying down?		
02.2.4	While resting later in the day?		

Appendix 2. WOMAC Assessment Questionnaire

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history/25046