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IMPROVEMENT IN PAIN RELIEF USING A DMSO BASED DICLOFENAC IN COMPARISON TO CONVENTIONAL DICLOFENAC GELS IN OSTEOARTHRITIS –A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT: Background: Topical NSAIDs are the first line choice of drug for management Osteoarthritis elderly patients, which produce less systemic exposure compared with oral NSAIDs. Now a day's several topical formulations are available. This study provides a comparison between two various topical diclofenac formulations. **Methods:** 12 weeks, randomized controlled trial to evaluate dimethyl sulfoxide (DMSO) based diclofenac solution and Linseed oil based diclofenac gel safety and efficacy profile. 43 men and women, age 40-65 years, with radiologically confirmed primary OA of the knee were included in this study. The included participants treated with DMSO based diclofenac solution; 40 drops 3 times daily directly to the painful knee without a massage (test group) and Linseed oil based diclofenac gel; 1 gram 3 times daily to the painful knee(control group). The primary outcome measure included the continuous variable pain relief and improved physical function measured by the Western Ontario McMaster Universities (WOMAC) Likert 3.1OA Index. Secondary efficacy measure was reduced stiffness. Safety assessment included adverse events and application site reactions. **Results:** DMSO based diclofenac solution group had a significantly greater mean change in score (final minus baseline) compared to the linseed oil based diclofenac gel group for pain (-9.8 *vs.* -6.9, p=0.032), stiffness (-3.7 *vs.* -2.4, p=0.048) and function, daily living (-26.4 *vs.* -15.9, p=0,019). Overall, each drug's application was well tolerated, and no adverse event was reported. **Conclusion:** This DMSO based diclofenac solution group showed statistically significant improvement in pain, stiffness and physical function compared to the conventional diclofenac gels.

INTRODUCTION: Osteoarthritis is characterized by pain, stiffness, cracking of the joints (crepitus) and loss of function of the joint which can lead to disability [1]. OA affects about 4-6% of the elderly population, and it is the leading top 5 chronic diseases in India [2].

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A survey-based study discloses that "India is forecast as chronic disease capital by 2025 has 60 million populations with arthritis". [3] Now itself no specific treatment available to cure the osteoarthritis, only symptomatic relief from the pain and stiffness of the knee. Primary management of OA for all individuals' medication is to reduce pain. Oral NSAIDs are recommended treatment for OA of the knee but have been associated with a higher risk in gastrointestinal, renal and cardiovascular systemic toxicity.

Current guidelines, Osteoarthritis Research Society International (OARSI) 2014 and National Institute

for Health and Clinical Excellence 2014 for the management of knee osteoarthritis recommends topical NSAIDs considered alternative to oral NSAIDs, cox-2 inhibitors or Opioid with decreased systemic exposure to the active diclofenac.

Topical NSAIDs are the safest medication and first-line therapy to OA management, especially in the elderly population, and those with co-morbidities such as HTN, type 2 diabetes mellitus, cerebrovascular or cardiovascular disease [4].

Objectives: In this report, we present the efficacy and safety results from a 12 week controlled trial to find out if there a difference in pain relief between DMSO based diclofenac solution and linseed oil based diclofenac gel. Our secondary objectives were to assess improvement in pain, stiffness and physical function in both groups.

MATERIALS AND METHODS:

Study Design: This study was a randomized controlled trial conducted from March 2018 to August 2018 at Maaruthi Medical Centre Hospital (MMCH), Erode. The ethical clearance was approved from Institutional ethics committee, and hospital authority has sanctioned, IEC approval number - EC NO/PHARM D/2018-6.

Participants (Inclusion / Exclusion Criteria): Participants were recruited from the MMCH orthopedic outpatient department. At the screening visit, all the patients gave informed written consent before their inclusion in this study. Inclusion criteria specified either gender; aged 40-65 years with primary OA of the knee defined as standard radiographic criteria for OA based on recent (within 3 months) examination and pain with regular use of topical NSAIDs. Participants were excluded if they had secondary arthritis like wrist, hip, feet and multiple joint osteoarthritis and history of major surgery, patients already on oral NSAIDs/analgesics, any contraindication to diclofenac, patients with skin wounds at the site of application, concomitant skin disease at site of application and severe cardiac, renal, hepatic or other systemic diseases; and history of drug or alcohol abuse.

Interventions: The participants were randomly divided into two groups in which test group (n=22) who get DMSO based diclofenac solution and control group (n=21) who get linseed oil based diclofenac gel with methyl salicylate. Test group participants were applied a dose of 40 drops DMSO based diclofenac solution (about 1.2 ml) to the affected knee 3 times daily up to 12 weeks and they were instructed to apply 10 drops of solution to each side of the knee (front, back, medial and lateral) dripped directly on to the affected knee and then spread over the site without massage. Control group participants have applied a dose of 4gm (4.5 inches) of gel on to the affected knee 3 times daily up to 12 weeks.

Outcome Measures: The primary outcome measures were defined as the change in from baseline to the final assessment of the study, knee in the 3 continuous variables pain, stiffness and physical functions measured by the Western Ontario McMaster Universities (WOMAC) subscales. There was no intermediate assessment of efficacy. The WOMAC pain scale validated questionnaire consisting of 24 questions, 5 questions on pain, 2 on stiffness and 17 on physical functions.

Each questions scored on a 5 point Likert scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme problem) [5]. Higher scores on the WOMAC indicate worse pain, stiffness and physical functions limitations [6].

Safety Analysis: Safety was assessed during every week clinic visit. Safety assessment included adverse event, application site dermatological reactions. Adverse events were identified using open questions and a checklist covering common oral NSAIDs side effects. Laboratory assessment was not done.

Randomization: A random number generator within Microsoft Excel will be used to generate the randomization sequence and maintained centrally by one of the investigators, who will not be involved in the assessment of participants.

Statistical Analysis: To find out the effectiveness of the drugs, the pain reduction between the two groups was compared by student independent "t" tests. To compare the two groups, they would be homogenous groups in respect of their demographic profiles. The homogeneity of discrete variables was tested by $\chi 2$ (Chi-square) test and

continuous variables by independent "t" test. The above statistical procedures were performed with the help of the statistical package IBM SPSS statistics-20. The level of significance was fixed as P-values less than or equal to 0.05 (P≤0.05).

RESULTS:

Participants Flow: 50 participants were randomized to treatment either DMSO based topical diclofenac solution (n = 26) or linseed oil based diclofenac gel (n = 24). All participants received their allocated intervention. Most of the participants completed this study (n = 43). The discontinuation rate due to non-availability during the study visit in both groups. Dropout due to lack of effect of treatment (n = 2), non-availability during the study visit (n = 5). Finally, n = 43 participants have completed this study in which test group (n = 22) and control group (n = 21) **Fig. 1**.

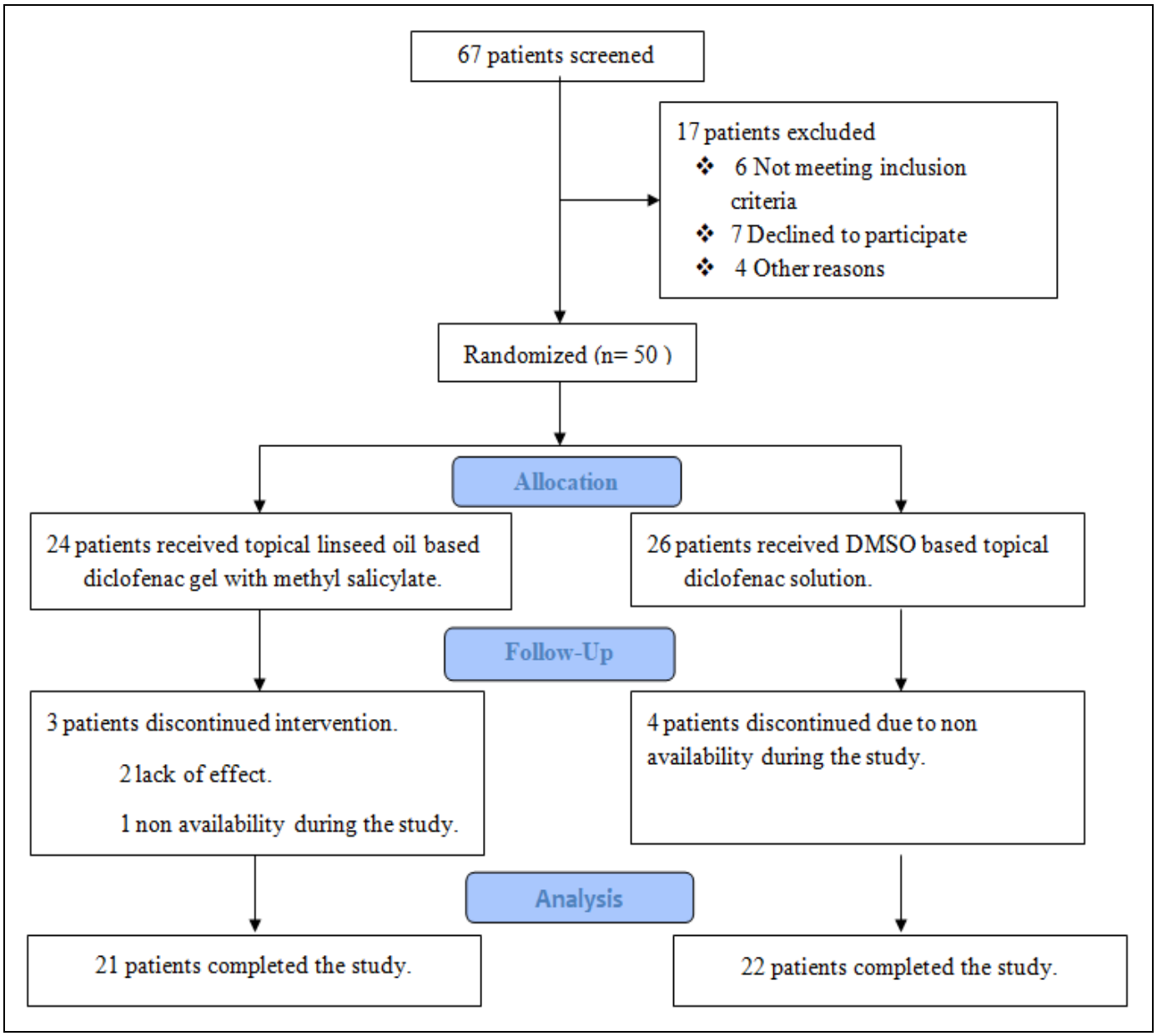

FIG. 1: FLOW OF PARTICIPANTS

Baseline Demographic Data: Table 1 states the description and homogeneity of the test and control groups. The demographic characteristics such as age, gender, BMI, number of knees affected, family history of OA, smoking status, co-morbid diseases, duration of OA, education status and occupation status of both groups were not statistically significantly differed (P>0.05). A summary of demographic data described in **Table 1.**

TABLE 1: DESCRIPTION AND HOMOGENEITY OF DEMOGRAPHIC PROFILES BETWEEN THE TEST AND CONTROL GROUP

Demographic profiles	Components	Test group n = 22		Control group n=21		Results	Significant
		No	%	No	%		
Age group (years)	40-49	6	27.3	9	42.8	Mean ± SD	P = 0.936
	50-59	10	45.4	3	14.4	53.4 ± 8.2	
	60-69	6	27.3	9	42.8	53.7 ± 9.1	
Gender	Male	7	31.8	11	52.4	χ^2 = 1.867	P = 0.172
	Female	15	68.2	10	47.6	df = 1	
BMI	Weight	62.0	11.0	66.5	13.5	t = 1.198	P = 0.238
(Mean ± SD	Height	156.6	9.4	158.1	13.0	t = 0.450	P = 0.655
	BMI	25.5	4.7	26.7	5.4	t = 0.836	P = 0.408
No of knees affected	Both knees	7	31.8	7	33.3	χ^2 = 0.011	P = 0.916
	Either knee	15	68.2	14	66.7	df = 1	
Family history of OA	Yes	6	27.3	4	19.0	χ^2 = 0.407	P = 0.523
	No	16	72.7	17	81.0	df = 1	
Smoking status	Yes	3	13.6	1	4.8	χ^2 = 0.227	P = 0.634
	No	19	86.4	20	95.2	df = 1	
Co morbid diseases	Yes	13	59.1	7	33.3	χ^2 = 2.865	P = 0.091
	No	9	40.9	14	66.7	df = 1	
Duration of OA (years)	Mean	6.5		5.3		t = 1.106	P = 0.275
	SD	3.8		3.1			
Educational status	Illiterates	7	31.8	5	23.8	χ^2 = 0.343	P = 0.558
	Educated	15	68.2	16	76.2	df = 1	
Type of occupation	Sedentary	12	54.5	11	52.4	χ^2 = 0.020	P = 0.887
	Heavy	10	45.5	10	47.6	df = 1	

Efficacy Outcomes:

The Effectiveness of the Drugs on Pain Relief: The effectiveness of the two drugs in pain relief within and between the two groups was compared. **Table 2** states the effectiveness of DMSO based diclofenac solution in pain reduction from baseline to last follow up. The mean pain on the baseline and last follow up was 11.1 ± 3.1 and 1.3 ± 0.7. The mean stiffness on the baseline and last follow up was 3.9 ± 2.2 and 0.1 ± 0.4. The mean physical function on the baseline and last follow up were 34.8 ± 13.5 and 8.4 ± 6.3. The mean total pain on the baseline and last follow up was 49.8 ± 17.8 and 9.9 ± 6.7. The differences between the above means were statistically very highly significant (P<0.001).

TABLE 2: PAIN REDUCTION WITHIN THE TEST GROUP FROM BASELINE TO the LAST FOLLOW-UP

Components (n=22)	Baseline		Last follow-up		Reductions		"t"	df	Significant
	Mean	SD	Mean	SD	Mean	SD			
Pain	11.1	3.1	1.3	0.7	9.8	3.3	13.795	21	P<0.001
Stiffness	3.9	2.2	0.1	0.4	3.7	2.1	8.247	21	P<0.001
Physical function	34.8	13.5	8.4	6.3	26.4	16.4	7.535	21	P<0.001
Total	49.8	17.8	9.9	6.7	39.9	21.1	8.877	21	P<0.001

Table 3 states the effectiveness of conventional diclofenac gel in pain reduction from baseline to last follow-up. The mean pain on the baseline and last follow-up were 11.2 ± 4.3 and 4.3 ± 2.8. The mean stiffness on the baseline and last follow up was 3.8 ± 2.2 and 1.4 ± 1.3. The mean physical function on the baseline and last follow up were 32.7 ± 13.6 and 16.8 ± 9.2. The mean total pain on the baseline and last follow up was 47.7 ± 18.9 and 22.4 ± 10.6. The differences between the above means were statistically very highly significant (P<0.001).

Table 4 compares the pain reductions between the two groups. The mean decrease in the test group was 9.8 ± 3.3 and control group mean reduction was 6.9 ± 4.9. The difference between the reductions was statistically significant (P<0.05). The stiffness reductions of test and control groups were 3.7 ± 2.1 and 2.4 ± 2.2. The difference between them was statistically significant (P<0.05). The mean reductions of physical function of both groups were 26.4 ± 16.4 and 15.9 ± 11.2. The difference of reduction between the two groups was statistically significant (P<0.05).

The total mean pain reductions between the test and control group were 39.9 ± 21.1 and 25.3 ± 14.8. The difference between the total mean reductions was statistically significant (P<0.05).

TABLE 3: PAIN REDUCTION WITHIN THE CONTROL GROUP FROM BASELINE TO LAST FOLLOW-UP

Components (n=21)	Baseline		Last follow-up		Reductions		"t"	df	Significant
	Mean	SD	Mean	SD	Mean	SD			
Pain	11.2	4.3	4.3	2.8	6.9	4.9	6.524	20	P<0.001
Stiffness	3.8	2.2	1.4	1.3	2.4	2.2	4.956	20	P<0.001
Physical function	32.7	13.6	16.8	9.2	15.9	11.2	6.493	20	P<0.001
Total	47.7	18.9	22.4	10.6	25.3	14.8	7.801	20	P<0.001

TABLE 4: COMPARISON OF PAIN REDUCTIONS FROM BASELINE TO THE LAST FOLLOW-UP BETWEEN TEST AND CONTROL GROUPS

Reductions	Test (n=22)		Control (n=21)		Difference b/w means	"t"	df	Significant
	Mean	SD	Mean	SD				
Pain	9.8	3.3	6.9	4.9	2.9	2.223	41	P=0.032
Stiffness	3.7	2.1	2.4	2.2	1.3	2.043	41	P=0.048
Physical function	26.4	16.4	15.9	11.2	10.5	2.435	41	P=0.019
Total	39.9	21.1	25.3	14.8	14.6	2.628	41	P=0.012

Safety Analysis: No adverse events were reported during the study period.

DISCUSSION: Published guidelines have incorporated topical NSAIDs as a recommended treatment for OA of the knee [5]. However, there has been controversy surrounding the adequacy of data is supporting their benefit beyond 12 weeks.

Total of 43 patients was enrolled and divided into two groups. Patients enrolled in both groups were comparable with each other to age, gender, BMI, no of knees affected, family history of OA, smoking status, co-morbid diseases, duration of OA, educational and occupational status with p>0.05 in all the groups, so difference between the two groups were not statically significant.

This present randomized controlled study evaluated the efficacy of the topical DMSO based diclofenac solution and conventional gel in the symptomatic treatment of OA of the knee. Efficacy findings demonstrated that for the primary endpoint (*i.e.,* WOMAC pain scale score from baseline to the final report of the pain scale score), patients reported significantly greater reductions in WOMAC pain scores with DMSO based diclofenac solution versus conventional gel (P=0.012). Moreover, improvement in the secondary outcome was also directionally and statistically significantly greater in the test group versus the control group as assessed under the study protocol; pain (p=0.032), stiffness (P=0.048), physical function (P=0.019). In general, the test group had a higher proportion of responders across the range of response levels shown compared with the control group. Analysis of all of the primary and secondary measures demonstrated that treatment with this topical diclofenac solution relieved the symptoms of primary knee OA at 12 weeks in this study population. Two other published trials using this DMSO based topical diclofenac solution showed it to be superior to vehicle control and placebo; a 4 week, non-flare trial [7] and a 12 week, flare trial [8].

The most common AEs with diclofenac topical solution analysis were application-site reactions [9]. The incidence of application-site reactions (29.0%) was greater than in recent studies of diclofenac sodium gel (5%-6% incidence) [10, 11] but was similar to that observed in previous placebo-controlled trials of diclofenac topical solution [7, 8, 12]. DMSO may produce skin dryness by dissolving lipids on the skin surface [13].

But in this study, no cutaneous AEs were reported because of the maximum of patients already exposed to topical diclofenac formulations. The safety analysis results in this study confirm topical NSAIDs had a lower incidence of gastrointestinal adverse events than the other formulations like oral tablets. The study has some limitations. It involved a small number of the population compared to the previous studies because there is no funding from another source. Trials were conducted over 12 weeks, which may not be including blood level safety analysis in this study.

Hence, only the efficacy data from these trials were reported here. No serious AEs were observed in this randomized trial in the general population.

However, confirmation of the CV safety of topical NSAIDs still warrants further study. Dosing compliance; Approximately 95% of patients self-reported >96% compliance by week 12; however, calculation of the difference between dispensed and returned study drug bottle weights showed that many patients administered lower than expected average doses in both treatment groups using the study drug dispensing system. Osteoarthritis is a major source of pain, disability and socioeconomic costs worldwide [24]. The DMSO based diclofenac solution has reduced pain and improved functions in the patients with OA and it is cost-effective than the conventional diclofenac gel.

CONCLUSION: DMSO based topical diclofenac solution symptoms relief knee OA over the 12 weeks. DMSO based diclofenac lead to significant improvement in pain, stiffness, and physical function scores, since the DMSO diclofenac has high tissue penetration in comparison to conventional diclofenac gel. The data in this and previous reports provide substantial evidence for the efficacy and safety of DMSO based topical diclofenac solution in chronic osteoarthritis.

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CONFLICT OF INTEREST: None declared.

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