Journal of Innovations in Pharmaceutical and Biological Sciences (JIPBS)
ISSN: 2349-2759
Available online at www.jipbs.com

Research article

A parallel arm interventional clinical Study to assess the efficacy and tolerability of ointment with natural ingredient in patients with chronic osteoarthritis of knee and low back ache

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Received on: 09/06/2022, Revised on: 05/07/2022, Accepted on: 10/09/2022, Published on: 17/09/2022.

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Keywords: Osteoarthritis, pain balm, VAS, herbal.

Vol. 9 (3): 06-11, Jul-Sep, 2022.

DOI:http://doi.org/10.56511/JIPBS.2022.9302

Abstract

Background: Treatment of OA focuses on reducing symptoms. Such treatment can be analgesic or nonsteroidal anti-inflammatory agents. With the current frequency and severity of adverse effects from analgesics and NSAIDs, suggestions for safer and sustainable interventions to manage the pain and stiffness are warranted. Natural local remedies, because of their relative safety, may reduce dependency on NSAIDs and analgesics and could have an important role in the treatment of OA. **Trial design:** Trial was parallel arm involving 60 patients with chronic osteoarthritis of knee and low back ache included in two parallel groups, Treatment Group (AVI- TR 01), and Control Group (n = 30/group). **Methodology:** The study involved assessment of changes in pain score with VAS, changes in WOMAC score, changes in severity of other symptoms like swelling, tenderness between treatment and control groups for the period of 14 days. **Results and conclusion**: It can be concluded that AVI- TR 01 treatment for pain and stiffness in patients with osteoarthritis by proving relief from pain, swelling, stiffness etc. It led to improvement in quality of life for the patients. There was reduction in the requirement of oral analgesics for the subjects using regular AVI- TR 01 for 14 days. Thus it can be concluded from the present study that the treatment with AVI- TR 01 is safe and effective solution to manage pain and stiffness in osteoarthritis.

Introduction

Osteoarthritis is related to increased health burden along with impairment in quality of life of an individual [1]. The occurrence of the population associated with aging, obesity along with joint injuries is becoming more common [2].

Osteoarthritis (OA) is a chronic, degenerative disorder characterized by gradual loss of cartilage in joints resulting in stiffness, pain, and impaired movements of knees, shoulders, hips, hands, feet, and spine. The disease is associated with risk factors such as obesity, lack of exercise, genetic predisposition, bone density, occupational injury, trauma, and gender [3]. Primary osteoarthritis is related to aging while the secondary arthritis usually occurs upon injury, diabetes, and obesity [4].

Treatment of OA focuses on reducing symptoms. Such treatment can be analgesic or nonsteroidal anti-inflammatory agents. Those present significant adverse effects, hence safer and sustainable interventions to manage the pain and stiffness are always needed [5, 6].

Use of natural ingredient as a topical application may provide systemic safety and may reduce dependency on NSAIDs and analgesics and could have an important role in

the treatment of OA. Topical ointments for pain and stiffness relief are always of choice as they are safe, not providing systemic adverse effects, convenient, avoiding drug interactions in comorbid patients and providing instant relief with improvement in quality of life for OA patients. There are many ointments for pain reliefs are available over the counter but most of them lack the clinical validation.

We proposed AVI- TR 01 ointment, which consists of natural oils from potent natural ingredients like Gaultheria fragrantissima, Eucalyptus globulus, Cinnamomum zeylanicum Cinnamomum camphora, Mentha piperita, Cedrus deodara and Boswellia serrata which have analgesic and anti-inflammatory properties. The ingredients in the formulation may serve as a precisely tailored therapy for the symptomatic treatment of OA. The existing literature and available scientific references to the ingredients of the AVI-TR 01 ointment indicate that it can synergistically support pain management and provide flexibility.

Therefore, the current study was conducted to clinically validate the safety and efficacy of the AVI- TR 01 ointment in OA patients. The outcomes are depicted and interpreted subsequently.

Study objectives

The primary objectives were assessment of changes in pain score with VAS, changes in WOMAC score, changes in severity of other symptoms like swelling, tenderness. The secondary outcomes were the Assessment of quality of life (QoL), changes in in requirement of analgesics as a rescue medication and assessment of patient compliance, adverse events etc.

Inclusion criteria

Male and female subjects aged 30 to 65 years with knee and back pain for at least 3-6 months with score on VAS more than or equal to 4 suffering from joint discomfort for at least 3 months duration were considered for the study. Subjects agreeing to discontinue any use of analgesics during the study were recruited. Analgesics were used as a rescue medication upon pain regression and investigator discretion. Subjects ready to provide written informed consent and willing to come for the follow-up visits for evaluation were included in study.

Exclusion criteria

Subjects with performed surgery for low back pain/ knee joint pain in the last 6 months or planning for surgical intervention during the course of the study were excluded from the study. Subjects with sensitive skin and damaged/ broken skin at the application site were not considered for the study. Subjects with secondary OA, such as due to injury, inflammatory condition, metabolic or rheumatic disease, osteonecrosis, Paget's disease, hemophilia etc. were not considered for the study.

Methodology

After attaining ethical approval, the study was registered on the CTRI website. The subjects were considered for further evaluation as per the inclusion and exclusion criteria. On the screening visit, written informed consent was obtained from those willing to participate. Demographic details, medical, surgical, and treatment history, current medication, if any, were noted in the case record form (CRF), along with the vital signs (pulse, blood pressure, body temperature) for each subject, followed by detailed clinical examination.

The final 60 subjects were randomized to either of the two treatment arms. A screening window of 1-2 days was considered. The record of concomitant medication was properly maintained. The treatment was followed till day 14. Weekly assessment of treatment compliance, symptoms, quality of life questionnaire and VAS scale was performed. All the subjects were advised for stopping analgesics through oral route. Oral analgesics were allowed as rescue medication upon investigator discretion. The presence of any adverse events was strictly monitored and reported. On day 14, all symptomatic and questionnaire based assessment was performed. After completion of the study period, the treatment of the subjects were continued as per investigators discretion.

Intervention and dosage

AVI- TR 01 ointment, consists of oils from potent natural ingredients like *Gaultheria fragrantissima, Eucalyptus globulus, Cinnamomum zeylanicum, Cinnamomum camphora, Mentha piperita, Cedrus deodara* and *Boswellia serrata* which have analgesic and anti-inflammatory properties. AVI- TR 01 was applied in sufficient amount to the affected area and massaged gently twice a day for 14 days.

Sample size

Change in mean pain VAS score between groups

Mean hemoglobin levels in control group = 4.86

Mean hemoglobin levels in test group = 1.75

2-side significance level = 0.05

Power (1-beta) = 0.95

N = 30 in each group

Based on above assumptions a sample size of Total 60 (30 cases in each arm) completed cases needed to assess the study objective at 90% power and 5% level $\Delta = |\mu 2-\mu 1|$ = absolute difference between two means

$\sigma 1$, $\sigma 2$ = variance of mean #1 and #2

n1 = sample size for group #1

n2 = sample size for group #2

α = probability of type I error (usually 0.05)

β = probability of type II error (usually 0.2)

z = critical Z value for a given α or β

k = ratio of sample size for group #2 to group #1of significance.

Randomization

We screened 65 participants based on the above-mentioned inclusion/exclusion criteria, of which 60 participants were found suitable for inclusion in the study. They were randomized using a computer-generated randomization sheet to receive either in the control group, or to the treatment arm (AVI- TR 01), where the patients were treated with AVI- TR 01 ointment.

Statistical analysis

Patients without any major protocol violation were included in the per-protocol population (pp), including those who had good treatment compliance, and those who did not take any prohibited medications during the study period with completed CRF. Both descriptive and inferential analyses were used for inferring the data. All p-values were reported based on a two-sided significance test and all the statistical tests were interpreted at a 5% level of significance.

Continuous variables, such as age and other demographical characteristics, were summarized by using summary statistics, i.e. frequency, and mean, and standard deviation. Categorical values like gender and clinical examination were summarized using frequencies and percentages.

No. of subjects responders for particular symptom were analyzed using Fisher Exact test and mean VAS score etc. by student t test.

Results

Demographic characteristics

Both groups were comparable in terms of the mean age of the male and female subjects (Table 1). The male to female ratio in both test and control groups was kept as 1:1.

Change in the clinical symptoms

Clinical symptoms, such as inflammation, swelling and flexibility were assessed on scale of 1-4, 1- no symptom, 2- mild, 3- moderate and 4- severe symptoms. The within-group analysis revealed a significant improvement in subjects experiencing no swelling and stiffness i.e. mild and moderate symptom subjects got shifted to no symptom score ($p<0.05$) in AVI- TR 01 group. There was not significant improvement in symptoms from control group (Table 2). However, it was evident that the AVI- TR 01 group had a faster relief of symptoms onset of action was within 30 minutes and considerable improvement in symptom score got demonstrated in 14 days.

Changes in VAS score between groups

The average VAS score for AVI- TR 01 and control groups were 7.9 and 7.57 respectively. The % reduction in AVI- TR 01 treated group was around 29 % and that of control was 15.41 %. There was more reduction in pain in AVI- TR 01 treated group than control (Table 3).

Changes in WOMAC score between groups

The baseline WOMAC score for AVI- TR 01 and control groups were 50.3 and 50.03 respectively. There was significant reduction in AVI- TR 01 treated group than control in 14 days. There is 17% reduction in WOMAC score in AVI- TR 01 treated group compared to 1.4% in Control group (Table 4).

Changes in SF-36 score (Quality of life score) between groups

There were comparable SF-36 scores between both groups at baseline. There was significant increase in quality of life in AVI- TR 01 treated group than control group.

Requirement of analgesics as rescue medication

In the control group, around 60% subjects (18 subjects) required analgesics as rescue for at least twice in a week. In AVI- TR 01 treated group around 40% i.e. 12 subjects required analgesics as a rescue medication (Table 5).

Table 1. Demographic details of the subjects

Parameter	Treatment		Control	
Group	Male (N=15)	Female (N =15)	Male (N =15)	Female (N =15)
Age (years)	44.4 ± 8.99	41.56 ± 8.51	49.56 ± 10.36	43.5 ± 9.01

Table 2. No. of subjects experiencing the scores between groups

Groups	Parameter/ Score	No. of subjects with score (4-severe, 3-moderate 2-mild 1-none)								P value
		Baseline				Day 14				
		1	2	3	4	1	2	3	4	
AVI- TR 01 (N=30)	Swelling	0	0	8	22	5*	10	15	0	0.05
	Joint flexibility	0	0	17	13	10*	10	10	0	0.0008
Control (N=30)	Swelling	0	0	17	13	0	0	14	16	1
	Joint flexibility	0	0	10	20	0	0	18	12	1

Data analyzed by Fisher exact test. * Significant between groups, significant at $p<0.05$.

Table 3. Changes in VAS score between groups

(Mean ± SD) VAS Score			
Duration	**AVI- TR 01 (N=30)**	**Control (N=30)**	**P value**
Baseline	7.9±1.09	7.57±1.14	0.2515
Day 7	6.07±1.48	6.43±1.43	
Day 14	5.67±1.30	6.40±1.33	
Mean diff (Baseline – Day 7)	1.83±2.17	1.13±2.15	0.210
Mean diff (Baseline – Day 14)	2.23±1.96	1.17±1.90	0.036
(p value)	<0.001	0.0007	

Within group analysis by ANOVA Tukey HSD and between groups by unpaired student t test. Significant at p<0.05.

Table 4. Changes in WOMAC score between groups

(Mean ± SD) WOMAC Score			
Duration	**AVI- TR 01 (N=30)**	**Control (N=30)**	**P value**
Baseline	50.3±3.68	50.03±3.23	0.7665
Day 7	45.37±2.89	48.6±4.02	
Day 14	41.7±1.60	49.33±2.99	
Mean diff (Baseline – Day 7)	4.93±3.73	1.43±4.82	0.0026
Mean diff (Baseline – Day 14)	8.6±3.64	0.70±4.10	<0.001
(p value)	<0.001	0.2775	

Within group analysis by ANOVA Tukey HSD and between groups by unpaired student t test. Significant at p<0.05.

Table 5. Changes in SF-36 score (Quality of life score) between groups

(Mean ± SD) SF-36 Score			
Duration	**AVI- TR 01 (N=30)**	**Control (N=30)**	**P value**
Baseline	16.4±1.75	15.93±1.89	0.3259
Day 14	28.8±1.35	20.4± 8.26	
Mean diff (Baseline – Day 14)	-12.4±2.16	-4.47±7.96	<0.001
(p value)	<0.001	0.0045	

Data analyzed by student t test. Significant at p<0.05.

Adverse events

No adverse events related to study medication or possible engagement of test intervention were reported throughout the study period.

Discussion

Limitations in the conventional medical management of osteoarthritis indicate a real need for safe and effective treatment of osteoarthritis patients. Thus, herbal medicines may give a direction of resolving this problem [7].

Phytoconstituents are known to play a major role in the management of arthritis. Considering the limitations of the conventional treatment for the management of OA, a polyherbal topical formulation conceptualized to be safe and effective in the management of Osteoarthritis. The present clinical study was conducted on 60 subjects (30 subjects in each group) suffering from osteoarthritis of the Knee(s) and lower back ache. Subjects were divided in two groups equally. One group received the AVI- TR 01 ointment for topical application and control group only followed their usual rescue medication as analgesics. The treatment was provided for 14 days and follow up scheduled on weekly basis.

Following are the broad outcomes of the present study of AVI- TR 01 ointment in subjects with knee osteoarthritis and lower back ache.

In the present study, subjects experienced swelling and frozen joints i.e. reduced flexibility to moderate to severe level. Slowly in the first week there was shift of subjects experiencing severe symptoms to moderate scale and

eventually till day 14, more and more subjects were experiencing only mild to no pain and stiffness. It can be concluded from the observations that, there was significant reduction in swelling around knee joints and significantly improved joint flexibility.

At baseline, in all subjects the pain was moderate in knee joints and lower back. Eventually after 14 days there was significant reduction in VAS score for pain. . The % reduction in AVI- TR 01 treated group was around 29 % and that of control was 15.41 %. There was more reduction in pain in AVI- TR 01 treated group than control.

WOMAC score represents degree of limitation to physical activities due to pain and stiffness due to osteoarthritic changes in joints and related muscle stiffness [8]. In the resent study, there is 17% reduction in WOMAC score in AVI- TR 01 treated group compared to 1.4% in Control group. That means there was improved flexibility and thus reduced limitations to physical activities in AVI- TR 01 treated group than control.

The osteoarthritis presents physical, emotional and social limitation to individual's lifestyle and thus reduction in the quality of the life (QoL). Chronic osteoarthritis present the reduced quality of life complicated with stress and depression. It is important to improve on the quality of life of subject to achieve the therapeutic goals in osteoarthritis [9]. In the preset study, we assessed SF-36 scale for quality of life assessment of trial participants. It was observed from the data collected that, there was 75% improved QoL score in AVI- TR 01 treated group compared to 28.06% in Control group.

The major concern of pharmacotherapy in osteoarthritic pain management is of side effects and the dependency. It is clinically relevant fact that the chronic use of analgesics may be nephrotoxic and lead to chronic renal failure. It is always advisable to incorporate the pharmacotherapeutic agents from natural source which can reduce the usage of analgesics in patients with chronic osteoarthritis. In present study, we ascertain to have this effect. In the control group, around 60% subjects (18 subjects) required analgesics as rescue for at least twice in a week. In AVI- TR 01 treated group around 40% i.e. 12 subjects required analgesics as a rescue medication.

No adverse events related to study medication or possible engagement of test intervention were reported throughout the study period.

From the evidences obtained through the present study, it can be concluded that AVI- TR 01 is safe and effective alternative in the management of pain in chronic osteoarthritis. The efficacy obtained of the AVI- TR 01 is by virtue of the ingredients used.

To summarize, there are three approaches by which AVI-TR 01 can prove as a good candidate be integrated into the management protocol of osteoarthritis. First, offering speedy clinical recovery to reduce pain and stiffness. Second, the combination shows significant anti-inflammatory potential to improve prognosis. Lastly, the potential to provide improvement in quality of life and reduced dependency on analgesics as rescue.

Conclusion

It can be concluded that AVI- TR 01 treatment for pain and stiffness in patients with osteoarthritis by proving relief from pain, swelling, stiffness etc. It led to improvement in quality of life for the patients. There was reduction in the requirement of oral analgesics for the subjects using regular AVI- TR 01 for 14 days. Thus it can be concluded from the present study that the treatment with AVI- TR 01 is safe and effective solution to manage pain and stiffness in osteoarthritis.

Acknowledgments

The authors would like to acknowledge the research team and the back-office team involved in the research work. We would like to acknowledge the monetary and material support provided by MN Pharmaceuticals, India.

Declaration of conflict of interests: None

Funding: Supported by MN Pharmaceuticals, India

Authors Contribution

All the authors have contributed equally in designing, drafting the manuscript as per the journal submission format. All authors read and approved the final manuscript.

References

1. Prieto-Alhambra D, Judge A, Javaid MK, Cooper C, Diez-Perez A, Arden NK. Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints. Annals of the rheumatic diseases. 2014; 73(9):1659-64.
2. Hunter DJ, Schofield D, Callander E. The individual and socioeconomic impact of osteoarthritis. Nature Reviews Rheumatology. 2014; 10(7):437.
3. Runciman WB, Hunt TD, Hannaford NA, Hibbert PD, Westbrook JI, Coiera EW, Day RO, Hindmarsh DM, McGlynn EA, Braithwaite J. CareTrack: assessing the appropriateness of health care delivery in Australia. Medical Journal of Australia. 2012; 197(2):100-5.
4. Pal CP, Singh P, Chaturvedi S, Pruthi KK, Vij A. Epidemiology of knee osteoarthritis in India and related factors. Indian journal of orthopaedics. 2016; 50:518-22
5. Tramèr MR, Moore RA, Reynolds DJ, McQuay HJ. Quantitative estimation of rare adverse events which follow a biological progression: a new model applied to chronic NSAID use. Pain. 2000; 85(1-2):169-82.
6. Weinberger M, Tierney WM, Booher P, Katz BP. Can the provision of information to patients with osteoarthritis improve functional status?. A randomized, controlled trial. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 1989; 32(12):1577-83.
7. Long L, Soeken K, Ernst E. Herbal medicines for the treatment of osteoarthritis: a systematic review. Rheumatology. 2001; 40(7):779-93.

8. Nerys F. Woolacott, Mark S. Corbett, Stephen J. C. Rice, The use and reporting of WOMAC in the assessment of the benefit of physical therapies for the pain of osteoarthritis of the knee: findings from a systematic review of clinical trials, *Rheumatology*, Volume 51, Issue 8, August 2012, Pages 1440–1446, https://doi.org/10.1093/rheumatology/kes043
9. Ware JE Jr, Keller SD, Hatoum HT, Kong SX. The SF-36 Arthritis-Specific Health Index (ASHI): I. Development and cross-validation of scoring algorithms. Med Care. 1999; 37(5 Suppl):MS40-50. doi: 10.1097/00005650-199905001-00004. PMID: 10335742.