CLINICAL STUDY

Natural Plant-Based Topical Cream RA-11(O) or Artrex® Significantly Improves Pain, Swelling, and Movement in a Randomized Clinical Trial in Osteoarthritis of the Knee

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ABSTRACT

Osteoarthritis (OA) affects millions of people worldwide. It causes severe pain, swelling, and stiffness, especially of the weight-bearing joints and hands, and aggravates with age and activity. Here we describe a unique, natural topical cream, RA-11(O) or Artrex® made up of seven Ayurvedic essential plant oils known to have multi-targeted anti-inflammatory and analgesic properties. After toxicity testing, a multicentric, double-blind, placebo-controlled clinical trial was conducted with RA-11(O) to study its effect on knee pain in OA patients. Out of 96 enrolled subjects with knee pain (Visual Analog Scale [VAS] score for pain >40 mm), 80 subjects completed the trial. Each applied the cream thrice daily for 14 days, with no other oral or topical analgesic drugs. There was significant reduction of pain in active compared to placebo cream on Day 7 ($p < 0.05$) and Day 14 ($p < 0.05$). Secondarily, a significant decrease in swelling, tenderness, and improvement of movement was also seen in subjects treated with RA-11(O) at the end of 14 days ($p < 0.001$). Global assessments from both physicians and patients showed significant improvement in all anti-inflammatory parameters. Thus, Artrex® is an effective plant-based cream for the relief of OA knee pain, and similar results are expected in hand and hip joints of OA.

Keywords: Ayurveda, osteoarthritis, knee, ginger oil, rose oil, joint pain, Artrex® cream, inflammation, mobility

Joint pain and swelling are very common complaints presented by adult subjects in any general outpatient department. Osteoarthritis (OA) is the most prevalent form of arthritis with significant impact on daily activity and work, including sleep and everyday life. It mostly affects the knees, hips, and hands, and can manifest in other joints of the body. According to the Global Burden of Disease Study 2021, there was a 132% increase in the number of OA cases worldwide in 2020 compared to 1990[1]. The condition most commonly manifests as pain in the weight-bearing hip or knee joints. OA places a significant economic burden on health care systems globally, costing billions of dollars each year. It is currently recognized as the third most rapidly increasing cause of disability, following diabetes and dementia. In India, the prevalence of knee OA is 47%; or almost half the elderly population in India suffer from OA of the knee, causing significant challenges to the health care system and economy[2]. In the United States, the Centers for Disease Control and Prevention (CDC) estimates that 1 in 5 or 53.2 million US adults are living with OA. In 2020, 595 million people worldwide had OA, which translates to 7.6% of the global population[1]. The majority of cases occur in people aged 45 and older, with women accounting for approximately 62% of those affected.

OA is a result of wear and tear or degeneration leading to joint fluid deficiency and severe inflammation. Such multi-targeted pathogenesis is exacerbated by inflammatory mediators such as cyclooxygenase, cytokines, adipokines, chemokines, and some matrix metalloproteinases. There are many drugs available to treat OA, most common being anti-inflammatory agents like nonsteroidal anti-inflammatory drugs (NSAIDs).

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Although these drugs can relieve the pain very well, their long-term use can cause severe health issues like gastrointestinal problems, renal, cardiovascular, and liver dysfunction[3].

Medicinal oils have been used for hundreds of years in the science of Ayurveda for management of joint pain and swelling. Today, specialized centers have grown all over the world offering "*Panchakarma Chikitsa*", which entails use of medicated oils and pastes for various ailments and beautification. However, due to inherent limitations of administration, staining and odor, the use of these oils in places other than institutionalized settings is cumbersome.

Given the aging global populations, and for better quality of life and mobility, we developed a novel topical cream from seven all natural herbal oils to fight pain faster, and in a more efficient and long-lasting way. We used classic camphor (*Camphora officinarum*), menthol (*Mentha piperita*), and turpentine (*Pinus longifolia*) oils, and added a proprietary mix of pure ginger oil (*Zingiber officinale*), methyl salicylate (Oil of Wintergreen), thymol (*Ptychotis ajowan*), and cinnamon oil (*Cinnamomum zeylanicum*) as unique anti-inflammatory agents. Rose oil, lemongrass oil, and eucalyptus oil were added for their skin soothing, emollient, and fragrant properties. We then tested our formulation in different skin safety and penetration assays. Once standardized, we herein report for the first time a double-blind, placebo-controlled trial of this cream on knee arthritis. Subjects were recruited as per the Institutional Review Board (IRB) approved protocol and all studies were done under strict Ethics Committee supervision and approval.

RA-11(O) with 41% essential oils is an attempt to provide the benefits of medicinal oils in a dosage form that is esthetically appealing and acceptable for use all over the world. Inspite of the high percentage of medicinal oils, the cream does not leave behind any stains or residue and has a pleasant odor. The pH limits for standardization of the cream were set at 4.0 to 7.0 and viscosity limit at 4,000 to 4,500 cps. The formulation has been standardized phytochemically using gas chromatography for quantification of the major ingredients i.e., menthol, camphor, and turpentine oil; high performance thin layer chromatography pattern for batch-to-batch comparison of finished product and total volatile oil determination for percentage of oils. The cream was studied for acute dermal toxicity in rats, and also for acute dermal irritation in rabbits using the modified Draize test (US EPA Health Effects Test Guidelines, 1998)[4]. These studies showed no dermal toxicity and zero skin irritancy score, respectively (unpublished data). All animal testing was conducted ethically under strict Organization for Economic Co-operation and Development (OECD) guidelines. This herbal oil-based formulation was then tested in an open label 14-day trial in patients with non-specific bone and joint pain, and showed significant improvement of pain and swelling[5]. Subsequently, the current double-blind, placebo-controlled trial was planned to test the efficacy and safety of this cream in terms of relief from pain, decrease in swelling and tenderness, and improvement in range of motion in subjects with symptomatic early OA of the knee joint. All oral and topical analgesic and anti-inflammatory drugs were strictly restricted during the course of the study.

MATERIAL AND METHODS

RA-11(O) contains natural plant-based essential oils. Its main active ingredients are camphor (*Camphora officinarum*), menthol (*Mentha piperita*), and Ayurvedic turpentine oil (*Pinus longifolia*), along with a blend of other essential oils such as ginger oil, thymol, wintergreen oil, eucalyptus oil, lemongrass oil, cinnamon oil, and rose oil. All oils and additional ingredients were sourced from a local supplier (Tripathi Herbs, Pune, India) and were of the highest available purity.

The oil and water phases were heated separately to a controlled temperature, then combined through fine filtration with continuous stirring to ensure uniform emulsification. The mixture was held at this temperature for at least 30 minutes, and then cooled to around 40°C. A blend of additional ingredients, including volatile oils, was added slowly under stirring. The emulsion was further cooled over 90 minutes to ensure complete dispersion. No organic solvents were used, ensuring a clean and stable product.

The final product was an off-white, aromatic, semi-solid cream with a viscosity of 4,000 to 4,500 cps at 25°C and a neutral pH, suitable for topical application. Active components – Menthol (5%), camphor (2%), and turpentine oil (10%)—were measured by gas chromatography. It was then cured overnight, and then packed into laminated tubes of 30 g. Placebo tubes were made exactly the same way without any active essential oils and packaged into tubes of the same size.

Study Design and Overview

A randomized, multicentric, double-blind, placebo-controlled trial was planned as per standard IRB protocol and Ethics Committee approval. A total of 112 persons with knee pain and swelling were screened, of which

96 subjects were included in the study. Subjects were enrolled after signing of informed consent form provided by the study sponsor. Detailed history and examination of subjects took place on site and baseline assessment of pain, swelling, tenderness and Visual Analog Scale (VAS) was noted. A skin irritation test was done on site. After randomization, all selected subjects were sent home with two tubes of trial medication, RA-11(O) or the placebo cream base (without any actives) for application on affected knee joint for 14 days. The subjects were advised to apply approximately 950 mg or 4 pea sizes of the cream (freshly taken out from the tube provided by the sponsor), thrice daily, with or without hot fomentation and gentle rubbing.

Eligibility criteria of the study were subjects aged 40+ years, of any gender and able to understand and sign the informed consent form and meet the inclusion criteria as approved by the Ethics Committee. A strict inclusion criterion was maintained as pain and swelling of one or both knees and some kind of restriction of movement of joint.

A stringent exclusion criterion was followed to keep the study population as close as possible. Patients with history of significant collateral ligament, cruciate ligament or meniscal injury requiring non-weight-bearing, any medical or arthritic disease (e.g., rheumatic/rheumatoid arthritis, entrapment neuropathy, vascular disease) that could confound or interfere with evaluation of pain or efficacy, inability to understand and complete study questionnaire were excluded from the study. Patients with a history of intra-articular injection of hyaluronic acid or corticosteroids into study joint within 3 months prior to first visit were also not included in the study. Most importantly, anyone on sustained use of NSAIDs was strictly excluded from the study. All such treatments had to be discontinued before study entry for at least 2 weeks before application of study medication. No other herbal or allopathic treatment, which could influence the outcome of the study, was permitted during the study. This included all prescription and over-the-counter analgesic, anti-inflammatory, and immunomodulatory agents. All other concomitant drugs taken during the study were recorded in the Case Record Form.

After initial evaluation, first visit was after 7 days of application where subjects were examined thoroughly with standardized VAS score as described for Day 1. Subjects were assessed for pain, swelling, and tenderness of study joint, and monitored for skin changes. Any other adverse effects were noted after repeated applications.

Follow-up and final visit was done on Day 14 of the study. All the parameters as described earlier and any further irritation or side effects on the site of applications were monitored. On Day 14, a global assessment was carried out in blinded fashion by both subjects and investigators. This assessment was done by filling up a standard questionnaire as per protocol and divided into four distinct categories – No effect (Nil), Poor, Good, and Excellent. Both physician and patients/subjects put their responses in blinded fashion in the questionnaires. When all the subjects completed the study, they were unblinded and scored independently. They were supposed to return all unused materials to the respective clinic.

Withdrawal of subjects was allowed as participation in the study could be discontinued if any subject chose to do so, or significant protocol violation, or due to serious adverse experience, or development of intercurrent illness that would put the subject at undue risk.

Sixteen (active = 7, placebo = 9) subjects were dropped from the study analysis because they refused to come for follow-up visits. Of these, 6 subjects (active = 4, placebo = 2) had traveled to a distant place, 2 subjects treated with placebo returned the drug container the next day and said they did not wish to continue to participate in the study. The other subjects could not be contacted to note the reason for noncompliance (Fig. 1).

Study Treatment/Trial Medications

Study drug or the placebo drug was dispensed in two 30 g laminated collapsible tubes for each subject, which was marked with subject number and the study code. Everyone was advised to store the study drug or placebo tubes at room temperature (25^0C).

Treatment compliance and method of assessment: Compliance was monitored by direct enquiry and visual inspection of the returned container.

Safety Assessments

A skin irritation test of the study drug was performed after the subject was enrolled in the study. Circular fields of measurement each of about 1 inch diameter were marked out on the left forearm of a right-handed subject. A small amount (50 mg) of the study drug was then applied as a patch on the site and the skin reaction was measured after 15 and 30 minutes. Changes in skin temperature, color, and thickness were noted each time. The subject was instructed to come the next day for assessment of any delayed response. The site of therapy was examined at every visit for changes and any relation of the changes with exposure to sunlight was noted.

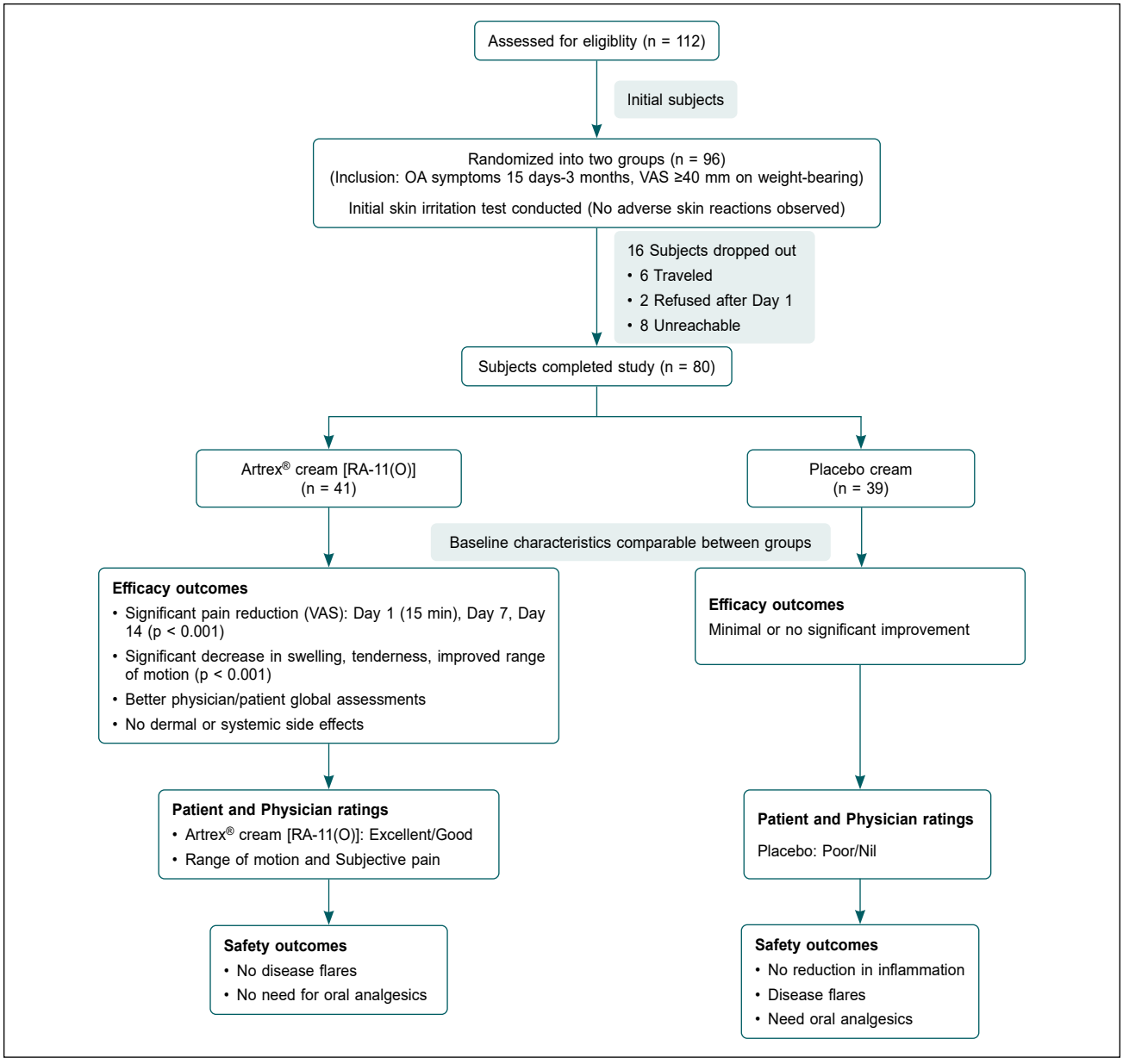

Figure 1. Flow chart.

Assessment of Efficacy and Safety

Clinical efficacy assessments were divided clearly into two categories. Primary endpoints were subjective improvement after application of study drug on pain relief and mobility. Objective changes were improvement or complete disappearance of swelling, moderate decrease or no effect. Pain assessment rating was done using pain VAS. Tenderness was assessed as present or absent. Secondary endpoints were defined as global impression by physician and patient, or any flares of disease or consumption of concurrent medicine for pain relief. Clinical safety assessment was done by observation of clinical signs and symptoms.

Statistical Analysis

Results were expressed as mean ± standard deviation (SD). Differences among groups were evaluated using one-way analysis of variance (ANOVA), with a significance threshold set at $p < 0.05$. Severity scores were also reported as mean ± SD, and signs and symptoms were assessed using a 0-4 grading scale.

RESULTS AND OBSERVATIONS

Sixty female and 20 male subjects completed the 14 days treatment and were included in the final analysis of the study. The active [subjects treated with RA-11(O)] and

Table 1. Characteristics of Patients at Study Entry (Baseline)

Variable	Active (n = 41)	Placebo (n = 39)	P value
Mean age (years)	50.07 ± 9.07	48.97 ± 8.80	0.58
Male : Female ratio	12:29	8:31	0.51
History of exercise (n)	25	20	0.51
Family history of musculoskeletal diseases (n)	6	3	0.53
Past medication history for joint pain (n)	18	14	0.61
Concomitant medication (n)	14	15	0.86
Body weight (kg)	61.48 ± 12.78	60.05 ± 12.63	0.61
Height (cm)	156.1 ± 9.9	158.8 ± 8.3	0.18
VAS for pain (cm)	6.09 ± 1.89	5.94 ± 1.65	0.71

the placebo [subjects treated with placebo] groups were well balanced in several of the demographic and other measures. The baseline characteristics of subjects are presented in Table 1.

The age, sex, past history, history of exercise, and family history were comparable in the subjects treated with RA-11(O) and placebo. The mean body weight of subjects treated with RA-11(O) was 61.48 kg at the first visit with a mean height of 156.1 cm. The mean body weight of subjects treated with placebo was 60.05 kg at the first visit with a mean height of 158.8 cm. The body weight of subjects in both groups remained constant and the vital parameters were all unaffected over the course of the study ($p > 0.05$).

Improvement on VAS at 15 minutes after application of drug was seen ($p = 0.028$) with decrease of 1.24 ± 1.42 in the active group and 0.61 ± 1.03 in the placebo group. The decrease in pain (VAS) was significant at Day 7 ($p = 0.01$) and Day 14 ($p = 0.01$) after treatment in the active group. There was a further decrease in pain VAS from the Day 7 to Day 14 ($p = 0.001$) in the same group (Fig. 2).

The other parameters of efficacy namely swelling, tenderness, restriction of range of movement, and subjective assessment of pain all showed significant improvement in the subjects treated with RA-11(O) as against those treated with placebo. The relief of pain as assessed by the subject 15 minutes after application of the drug on the first day of treatment was higher ($p = 0.005$) in the active group than in the placebo group.

The results of assessment of joint pain, swelling and tenderness, and range of motion at each follow-up visit are presented in Table 2.

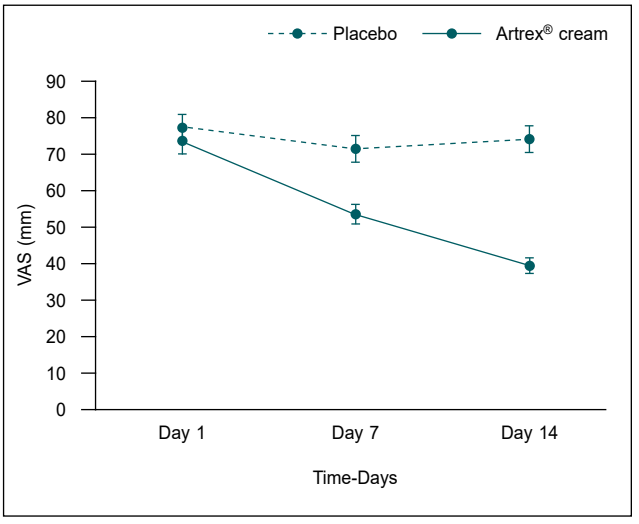

Figure 2. Visual Analog Scale for pain.

The physician's and patient's/subject's assessment of disease showed significant improvement at the end of 14 days in subjects treated with RA-11(O), and no improvement in subjects treated with placebo. The global impression of the physicians and patients/subjects are summarized in Figure 3.

Ten subjects described RA-11(O) as excellent and 30 rated it as good, as against all subjects treated with placebo rated the medicine as poor to nil effect. The physicians described RA-11(O) as excellent in 7 cases and good in 33 cases. The placebo was observed to have only poor or nil effect of treatment.

No flares of disease (defined as increase in VAS by >30 mm) or requirement for oral analgesics were noted in any subject treated with RA-11(O). An increase in VAS by >30 mm at end of 14 days was seen in 2 subjects treated with placebo.

Table 2. Efficacy Parameters

Variable	Active (n = 41)			Placebo (n = 39)			P values
	Mild	Moderate	Severe	Mild	Moderate	Severe	
Swelling							
Day 1	18	16	2	23	12	0	0.93
Day 7	26	7	0	23	12	0	0.39
Day 14	14	0	0	22	13	0	0.001*
Tenderness							
Day 1	12	21	3	17	15	1	0.89
Day 7	22	6	0	23	8	1	0.24
Day 14	13	1	0	16	17	0	0.05*
Restriction of range of motion							
Day 1	15	2	0	12	0	0	0.44
Day 7	10	1	0	11	0	0	0.91
Day 14	4	0	0	12	0	0	0.03*
Physician's assessment of disease							
Day 1	5	20	16	4	27	8	1
Day 7	22	17	0	10	22	7	0.25
Day 14	24	3	0	4	25	10	0.01*
Patient's assessment of disease							
Day 1	5	18	18	4	27	8	1
Day 7	23	17	0	10	21	8	0.51
Day 14	23	3	0	6	24	9	0.001*

Values are number of patients reporting symptoms at each severity level.

P values calculated between groups at each time point.

*Indicates statistical significance.

Patients with no signs of disease were compared in the two groups using Chi-square test and Fisher exact test where Chi-square was not applicable.

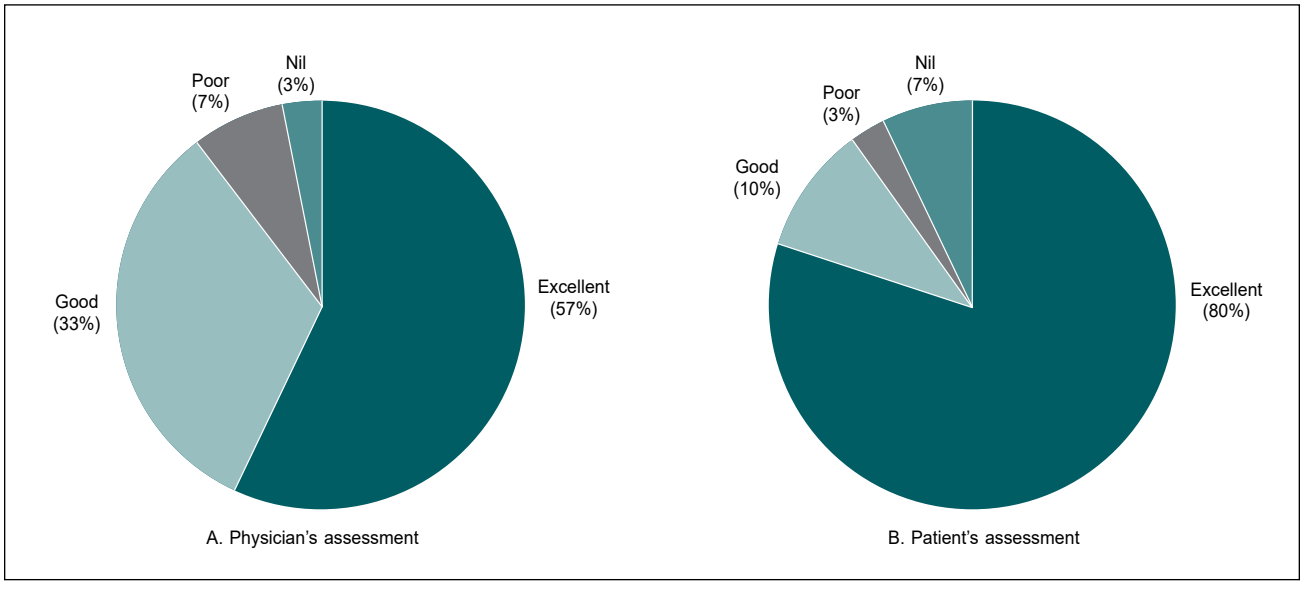

Figure 3. Global impression in active subjects.

DISCUSSION

This clinical study was conducted to validate the efficacy and safety of RA-11(O), commercially available as Artrex® cream. The major ingredients of RA-11(O) namely camphor, menthol, and turpentine oil, have analgesic and anti-inflammatory actions[5-7]. Camphor in addition gives a cooling effect. Menthol has antimicrobial properties, while thymol and eucalyptus oil are good counterirritants[8-12]. Turpentine oil has an unpleasant odor, which is well masked by the fragrances of rose oil, menthol, and camphor. Cinnamon oil has good penetrating action thereby increasing the bioavailability of other constituents of the cream[13]. Lemongrass oil, wintergreen oil, and ginger oil are specifically indicated as excellent anti-inflammatory agents for OA and other degenerative and inflammatory arthritic conditions[14-16]. Hence, RA-11(O) cream was expected to offer relief of joint pain and swelling in subjects with early OA. Elderly subjects, with signs and symptoms of early OA were included in the current study, and are representative of the pathogenesis and incidence in the worldwide population.[17] Immediate diagnosis and symptomatic treatment relieves pain and decreases the risk of long-term illness in these subjects[18].

The demographic details of subjects enrolled in the study show a significantly higher number of female subjects than males. The knee was the most commonly affected joint, followed by hip, ankle, shoulder, elbow, and finger joints. History of exercise was comparable in both subjects treated with RA-11(O) and in those treated with placebo.

The body weight, height of subjects, and vital parameters were constant during the course of the study. A high body weight-to-height ratio is a known risk factor for OA[19] and joint pain[20-23], and any influence of body weight on symptoms could be ruled out over the course of the study. No local drug reaction, a side effect of topical preparations[24] was noted in any subject. No photo-contact skin changes, a well-recognized side effect of topical analgesic preparations[25] were noted during the entire study duration in any subject.

There was a significant reduction in the VAS score for assessment of pain on both Day 7 and Day 14 in subjects treated with RA-11(O). Similar reduction in the pain (VAS) has been seen in studies on topical NSAIDs in joint injuries[26] as well as in OA[27]. The number of subjects with swelling on affected joint and tenderness was also decreased in subjects treated with RA-11(O). Subjects treated with placebo did not show any significant improvement of all tested parameters of efficacy.

The physician's and patient's/subject's assessment of disease showed significant improvement in those treated with RA-11(O). Similar encouraging assessments of disease by the patient/subject and physician have been observed and used for deriving the appropriate treatment in other clinical trials on topical anti-inflammatory agents[28]. The global assessments of the physician and patient/subject have been used as efficacy criteria in clinical studies involving topical anti-inflammatory drugs[29]. Both physician and subject global assessments showed excellent to good action of RA-11(O) and poor to no action of placebo. No flares of disease or requirement for oral analgesics[30] were noted in any subject.

There are limitations of this study. The test drug was compared with a placebo and not an active drug due to the dearth of well-controlled clinical studies of herbal topical drugs in pain management. Radiographic examination of all subjects was not possible and X-ray findings therefore could not be used to confirm the diagnosis of OA.

CONCLUSION

This controlled trial demonstrates the potential efficacy and safety of RA-11(O) in the symptomatic treatment of early OA of knees over 14 days of treatment. The domains of pain, freedom of movement and global assessment, which are the core variables in any study of OA joint pain, and swelling have all shown significant improvement with RA-11(O). In addition, this study has shown a rapid onset of action and long-lasting effect after application of the study product. The effect of RA-11(O) on pain and swelling of etiologies other than OA needs to be tested. This product, Artrex® cream thus offers a safe and effective cream for local application for relief of joint pain and swelling in subjects with early OA.

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