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Efficacy and safety of RA-11 (O) – A herbal analgesic cream

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The plant based multi-component formulation; RA-11 (O) has been conceived and developed from Ayurvedic science for topical application in patients with joints pain and swelling. The clinical study was undertaken to test the safety and efficacy of RA-11 (O). Thirty patients, who had joints pain and swelling, with restriction of movement, and were able to understand and sign the informed consent form, were included in the study. The patients were advised to apply the study drug thrice daily for 14 days. There was significant reduction in the Visual Analog Scale score for joints pain on 7th and 14th day ($p<0.001$). The physician's assessment of disease showed improvement with 9 patients being a symptomatic on 7th day of treatment and 25 patients being a symptomatic on 14th day of treatment. The patient's assessment of disease showed a similar resolution of symptoms with 6 patients noting no symptoms on 7th day of treatment ($p<0.01$) and 23 patients being a symptomatic on 14th day of treatment ($p<0.001$). Body weight and vital parameters were unaffected over the course of the study. Skin irritation test showed no irritation in any of the patients and no dermal side effects were observed on follow up over 14 days. The domains of pain, freedom of movement and global assessment, which are the core variables in any study of joints pain and swelling; showed significant improvement in the study. RA-11 (O) has been reported as a safe and effective topical cream for relief of joints pain and swelling.

Key words: Ayurvedic cream, Analgesic cream, Antiinflammatory cream, Herbal cream, Joints pain, Swelling

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Joints pain and swelling are common complaints presented by adult patients. Medicinal oils have been used for the management of joints pain and swelling by Ayurvedic experts[1,2]. However, the use of these oils in places other than institutionalized settings or centers offering *Panchakarma Chikitsa* is cumbersome, due to inherent limitations of staining and odour. RA-11 (O) with 41% essential oils is an attempt to provide the benefits of these natural medicinal oils in a dosage form that is acceptable for use. In spite of the high percentage of such essential oils, the cream does not leave behind any stains or residue and has a pleasant odour.

RA-11 (O) contains essential oils of *Mentha piperita* Linn. Emend Huds. (menthol), *Cinnamomum camphora* (Linn.) Nees & Eberm. (camphor) and *Pinus roxburghii* Sarg. (turpentine oil) as the active components. In addition, it contains essential oils of *Trachyspermum ammi* (Linn.) Sprague (thymol) *and Zingiber officinale* Rosc. (ginger), as inactive ingredients (Table 1).

Table 1—Composition of RA-11 (O)

Major ingredients	Percentage	Role
Camphor USP (*Camphora cinnamomum*)	5%	Analgesic
Menthol USP (*Mentha piperita*)	3%	Analgesic
Turpentine oil BP (*Pinus longifolia*)	10%	Analgesic

USP = United States Pharmacopoeia, BP = British Pharmacopoeia

The formulation has been standardized phytochemically using gas chromatography for quantification of the major ingredients, high performance thin layer chromatography pattern for batch-to-batch comparison of finished product, and total volatile oil determination for percentage of oils. The *p*H limits for standardization of the cream were set at 4.0-7.0, viscosity limit at 4,000 - 4,500 centi poise and total volatile oil contents at 33± 2%. The cream was studied for acute dermal toxicity in rats and also for acute dermal irritation in rabbits using the Draize test[3]. These studies showed no dermal toxicity and zero skin irritancy scores, respectively.

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Methodology

The study was conducted at a community healthcare center, Wadnap Hospital, Pune, after appropriate ethics committee clearance. Adult patients with joints pain, swelling and restriction of movement; who were able to understand and sign the Informed Consent Form were included in the study. The patients with history of joints injury requiring no weight bearing and intra-articular injections into study joint within 3 months prior to first visit were excluded from the study. No other herbal or allopathic treatment, which could influence the outcome of the study, was permitted during course of the study. The study drug, RA-11 (O) was dispensed in two 20 ml collapsible tubes that were marked with patient code and stored at room temperature (25°C). The patients were instructed to apply on the affected joints thrice daily with gentle rubbing for 14 days[4]. Direct inquiry and visual inspection of the returned container were used for monitoring compliance.

Detailed history and examination of patients, baseline assessment of pain, swelling, tenderness, Visual Analog Scale (VAS) (Appendix 1), skin irritation test and evaluation of relief 15min after application of drug were recorded at enrollment of patient. A circular field of measurement of 2.5 cm diameter was marked on the left forearm of the patient for skin irritation test. 50 mg of study drug was then applied as a patch on the site and changes in skin temperature, colour and thickness were noted after 15 & 30 min, and after 24 hrs. The patients were followed up on the 7th and 14th days. The Visual Analog Scale, assessment of pain, swelling and tenderness and the physician's and patient's assessment of disease were primary efficacy criteria[5]. The t-test was used for analysis of qualitative data and the Z-test for quantitative data.

Appendix – 1

Visual Analog Scale (VAS)-Pain Assessment Tool]

The VAS is designed as a 10cm line, with descriptors at each end

PATIENT'S ASSESSMENT OF PAIN

Indicate on the pain scale, the amount of pain you have today

No pain ——————————— Worst possible pain

The VAS for treatment effect:

Right knee

No pain ——————————— Worst possible pain

Left knee

No pain ——————————— Worst possible pain

The VAS is designed as a 10 cm line, with descriptors at each end. The VAS was scored by measuring from the patient's mark to the beginning of the scale in centimeters.

Results and discussion

Twenty six female and four male patients enrolled in the study completed 14 days of treatment. The baseline characteristics of patients are presented (Table 2). Thirteen patients had pain and swelling of knee joints, 6 complained of ankle pain and 3 each had shoulder and elbow pain. 2 patients had pain in hip joints following trauma and 1 each had backache, wrist pain, tennis elbow, cervical spondylosis and trauma to great toe. History of minor trauma or overuse of the affected joints was elicited in 13 patients with symptoms of acute onset. 9 patients had symptoms of longer duration. In other patients with symptoms like backache and knee pain, the duration of symptoms could not be elicited. 8 patients had symptoms in more than one joint. The joints with more severe symptoms at enrollment as judged by the baseline Visual Analog Scale score was used for analysis. The mean body weight of patients was 57.6 kg with a mean height of 149.3 cm. Skin irritation test showed no irritation in any patients and no dermal side effects were reported in follow up visits on 7th and 14th days.

Table 2—Characteristics of patients at study entry [N = 30]

Characteristics		Values
Mean age (yrs)		55.7 ± 9.5
Nature of exercise	Walking	14
	Yoga	1
Family history of musculo-skeletal diseases		4
Patients with symptoms <15 days		13
Patients with symptoms for 2 months		5
Patients with symptoms for 2-6 months		4
Duration unknown		8
Past medication history for joints pain	NSAIDs	12
	Steroids	2
	DMOAD/DMARD	0
	Ayurvedic	5
	Homeopathic	3
Concomitant medication	Diabetes mellitus	3
	Hypertension	2
	Deep vein thrombosis	1
Affection of more than one joint		8

NSAIDs = Non-steroidal antiinflammatory drugs, DMOA = Disease modifying osteoarthritis drugs, DMARD = Disease modifying antirheumatic drugs

Table 3—Change from baseline of continuous clinical efficacy measures (n=30)

Efficacy measures	1Day (No of patients)	7Day (No of patients)	*p* values	14Day (No of patients)	*p* values
Swelling	25	12	<0.001 (Z=3.45)	15	<0.001 (Z=5.16)
Tenderness	25	10	<0.001 (Z=3.9)	4	<0.001 (Z=6.5)
Physician's assessment of disease-number with symptoms	30	21	<0.001 (z=3.2)	5	<0.001 (Z=6.5)
Patient's assessment of disease-number with symptoms	30	24	<0.01 (Z=2.5)	7	<0.001 (Z=6.1)
VAS for pain (score) mean (95% CI)	4.86 (3.98-5.76)	1.7 (0.94-2.46)	<0.001 (t=8)	1.2 (0. 22-2.18)	<0.001 (t=8.3)

Quantitative 'Z' test

Table 4—Global impression

Impression	Excellent	Good	Poor	Nil
Physician's global impression (n=30)	17	10	2	1
Patient's global impression (n=30)	24	3	1	2

The results of assessment of joints pain, swelling and tenderness are presented (Table 3). None of the patients in the study showed an increase in the VAS score at any follow up visit. 10 patients showed an improvement in VAS score of more than 3 cm on 7th day, and 13 showed similar improvement on 14th day. The mean improvement seen after 15 min of application of RA-11 (O) for the first time was a VAS score for treatment effect at 3.5+1.9cm. The physician and patient global impressions of are summarized (Table 4). Body weight of patients remained constant and vital parameters were all unaffected over the course of study ($p>0.05$). No flares of disease or requirement for oral analgesics were noted in any patient.

This preliminary clinical study was conducted to validate the efficacy and safety of RA-11 (O). The major ingredients of RA-11 (O)-camphor (*Cimmamomum camphora*), menthol (*Mentha piperita*) and turpentine oil (*Pinus longifolia*), have analgesic and antiinflammatory actions[6,7,8]. Camphor in addition gives a cooling effect. Menthol has antimicrobial properties; thymol (*Ptychotis ajowan*) and ginger oil (*Zingiber officinale*) are good antiinflammatory agents and counter irritants, the latter being specifically indicated for rheumatoid arthritis[6,7,8]. Hence, RA-11 (O) cream was expected to offer relief in joints pain and swelling. The patient demographics in the study show a significantly higher number of elderly and female patients. The most commonly affected joints were knees followed by ankle, shoulder, elbow and hip joints. A study on prevalence of lower extremity pain and its association with functionality in elderly women has reported a higher incidence of knee pain followed by the hip and the foot[9]. History of exercise was limited to walking in 14 patients and yoga in 1 patient. Intensive exercise has been known to improve physical function and have a modest effect on pain[10]. This was, however, not observed in any of the patients before or during the course of the study.

Most patients in the study had minor trauma and overuse of affected joints. Immediate diagnosis and symptomatic treatment relieves pain and decrease the risk of post traumatic osteoarthritis in these patients[11,12]. Chronic degenerative disease was the most probable diagnosis in the other nine patients all above 50 yrs of age, with symptoms of longer duration[13]. Body weight, height of patients and vital parameters were constant in the course of study. A high body weight: height ratio is a known risk factor

for osteoarthritis and joints pain[14,15]. Any influence of body weight on symptoms was ruled out over the course of the study. No local drug reaction, a side effect of topical preparations, was noted in any patient[16]. No photo-contact skin changes, a well-recognized side effect of topical NSAIDS, were noted during the entire study duration in any patient[17]. There was a significant reduction in the VAS score for assessment of pain on both 7th and 14th days. Similar reduction in the pain Visual Analog Scale has been seen in studies on topical analgesics in joints injuries as well as in osteoarthritis[18,19]. The number of patients with swelling on affected joints and tenderness decreased by 7th day.

The physician's and patient's assessment of disease showed significant improvement. Similar encouraging assessment of disease by the patient and physician have been observed and used for deriving the appropriate treatment in other clinical trials on topical antiinflammatory agents[20]. Both these parameters showed a further reduction on 14th day as compared to 7th day. The global assessments of the physician and patient have been used as efficacy criteria in clinical studies involving topical antiinflammatory drugs[22]. Seventeen patients described the trial medication as excellent and 10 rated it as good. The physician described the medication as excellent in 24 cases and good in 3 cases. No flares of disease or requirement for oral analgesics were noted in any patient. Similar observation of absence of need for oral analgesic was made as an efficacy parameter in other clinical trials[21].

Conclusion

The domains of pain, freedom of movement and global assessment, which are the core variables of any study of joints pain and swelling, have all shown significant improvement with the study drug RA-11 (O) [23]. The drug, RA-11 (O) can therefore be used as safe and effective cream as local application for relief of acute joints pain and swelling.

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