

Comparison of effect of topical application of *Eugenia caryophyllata* extract and topical diclofenac in primary knee osteoarthritis: a clinical trial study

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Received: 18/May/2015 Accepted: 13/Oct/2015

ABSTRACT

Background and aims: Osteoarthritis is one of the most common arthritis in elderly. No confirmed cure is found for it and current treatments have only analgesic effect. In this study, it was evaluated to compare the effect of topical application of *Eugenia caryophyllata* extract and topical diclofenac and placebo in primary knee osteoarthritis.

Methods: This randomized double-blind clinical trial study was carried out upon 105 patients with primary knee osteoarthritis. Patients were selected randomly and divided into 3 groups. The first group was given three times 1 mg diclofenac 1% of one mg, the second group was given 1mg topical caryophyllata 10% of 1 mg three times daily and third group was given 1 mg placebo 1 mg three times daily. For three groups, WOMAC questionnaire

(overall pain, knee pain, morning stiffness, stiffness during day, physical activity) were completed pretreatment, one week and three and four weeks post-treatment. The data were analyzed by SPSS through ANOVA and chi-square tests.

Results: In this study, the data collected from 105 individuals were analyzed in 3 groups. The findings indicated that there is a significant decrease in overall pain (P=0.005), stiffness during day (P=0.001), morning stiffness (P=0.001) and knee pain (P=0.017) and physical activity (P=0.001) in four weeks after the initiation of treatment in three groups of topical *Eugenia caryophyllata*, diclofenac and placebo (P<0.001). In all the three groups, mean overall score of WOMAC questionnaire was significantly decreased (P<0.001). No side effect related to the intake of medication in 3 groups was observed.

Conclusion: Extract of *Eugenia caryophyllata* is effective in decreasing knee pain, morning stiffness, and stiffness during day and improvement of physical activity in patients with knee osteoarthritis and it can be used alongside of chemical medication to reduce symptoms of patients in knee osteoarthritis.

Keywords: Knee osteoarthritis, *Eugenia caryophyllata*, Placebo, Pain, Diclofenac.

INTRODUCTION

Osteoarthritis is the most common sort of arthritis that high level of disability resulting from disease put it at the top of

major causes of disability in elderly. Osteoarthritis often involved cervical and lumbar vertebrate and sacrum, hip, knee,

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first metatarsophalangeal joint, hands, the distal to proximal joints, and the thumb proximal.¹

Osteoarthritis is a disease with high heritability, but the rate of heritability is varied based on the joint. Heritability section of knee osteoarthritis is maximum 30%, but this pervasive osteoarthritis phenotype is rarely inherited, and it is mostly of the consequences of aging.² In the U.S, it is predicted that by 2020, the rate of prevalence of osteoarthritis will increase up to 66-100%.¹

In some countries as Iran, knee osteoarthritis is more common due to certain habits that cause pressure on the knee joint, and it also appears at an early age.³ Osteoarthritis can be also diagnosed based on clinical symptoms, physical examination and radiographic signs.⁵

The rate of prevalence of osteoarthritis has a significant relationship with age. Osteoarthritis is rarely occurred in adults under the age of 40 years and is very common in people aged more than 60 years. Radiographic evidence suggests that osteoarthritis is common in the low back and neck.^{1,3}

The presence of antioxidative material in the diet can prevent or delay osteoarthritis. Injuries result from reactive oxygen species show that the most important among them is Nitric oxide compounds. Progression of knee osteoarthritis in people who have vitamin C deficiency is 3 times higher than those with its high intake. Besides, vitamin D deficiency is associated with the further progress of radiological osteoarthritis.⁵

Carnation as a spice and medicine in Chinese and Hindi medicine is used in cases as toothache or rheumatism.^{6,7,8} Some researchers believe that the analgesic effect of *Eugenia caryophyllata* probably plays a function through inhibition of arachidonic acid metabolism

and inhibition of histamine secretion and in consequence, reduction of inflammatory response would occurs.⁹⁻¹¹ On the other hand, some researchers believe that eugenol and other similar compounds of capsaicin have similar function and their receptors place at the end of axons of primary afferents of posterior horn throughout the spinal cord and may apply analgesic effect of eugenol through this similarity.^{12,13}

According to the fact that eugenol derivatives have agonistic and blocking effect on the Adrenergic receptors and these receptors have important effect on Analgesic systems, it seems that besides peripheral inhibition of afferent fibers of pain, eugenol affects centrally spine and results in increases in analgesia.¹⁴

The best treatment for osteoarthritis is often obtained through trial and error and each patient shows idiosyncratic reactions to specific treatments. Gels or creams of topical medications containing analgesia or non-steroidal anti-inflammatory drug can be named.¹ Due to the properties and nature of Carnation and hot and dry vs. cold and wet nature of knee osteoarthritis and the increasing tendency of the people to medicinal herbs, it can be used as an alternative for Diclofenac. Therefore, this study aimed to compare the effect of topical application of *Eugenia caryophyllata* extract with topical Diclofenac and placebo of knee on knee osteoarthritis.

METHODS

This double-blind clinical trial study was carried out on patients with early knee osteoarthritis. The population of this study was the patients referred to educational clinic of Shahrekord University of Medical Sciences that were selected by non-probability sampling, under supervision of the orthopedic specialist in 2013.

The inclusion criteria were minimum age of 30 years and maximum age of 60 years with approved knee osteoarthritis, not relieved severity pain based on the clinical symptoms despite of regular medical treatment and examination for 3 months. Exclusion criteria was the existence of simultaneous severe diseases such as gastrointestinal and metabolic diseases, fluctuating doses of drugs during the study, severe infection, allergy to *Eugenia caryophyllata* extract, pregnancy, lactation, impaired liver tests. It should be noted that intra-articular injection of corticosteroids within 5 weeks does not cause any problem.

In this study, 120 patients were enrolled and were randomly divided into 3 groups of 40 patients. The first group used ointment of Carnation 10% with the dose of 1 mg. The second group used diclofenac 1% three times daily and the third group used topical ointment containing placebo 3 times daily and each time at a dose of 1 mg.

Not to find any problem for the patients during the study, analgesic-like drug like naproxen 500 mg was administered. According to the type of the study that was double-blind clinical trial, patients who received drug and orthopedist who prescribed the drug were not aware of the types of drugs administered to patients.

To achieve this purpose, having diagnosed and selected the patients by orthopedist, and the patient was referred to an individual and *Eugenia caryophyllata* and topical diclofenac and placebo ointment were randomly distributed between patients and each person was given a code and the codes were recorded in the predetermined tables and completed the number of patients. The codes and tables were returned to the related orthopedist. Extract of *Eugenia caryophyllata* plant was prepared in the

Research Center of Medicinal Plant in Shahrekord University of Medical Sciences and having weighed, it was prepared with the ointment 10% with paraffin and glycerol base. Topical diclofenac 1% and placebo ointment was taken from pharmacies with glycerin and paraffin base without any additive. All the patients were followed up for a month in 4 periods of time, including before treatment and one week and 3 and 4 weeks after receiving the ointment.

Follow-up was in a way that patients who were able to visit in person, come to the place otherwise they were followed via phone and WOMAC questionnaire was completed by patients at every turn. During follow-up, 14 subjects were excluded from the study. In addition to the WOMAC questionnaire, visual analogue score questionnaires (VAS score) were also completed in every turn of follow-up. WOMAC scales under study included the pain, stiffness intensity (Stiffness) immediately after waking up, stiffness after sitting, sleeping or resting, physical performance in different activities. The collected Data were analyzed by SPSS software using ANOVA and chi-square test.

Results

Of the 120 patients who participated in this study, 15 patients were excluded due to withdraw from the cooperation. The data related to 105 patients were finally analyzed. In diclofenac group (n=35), 62.9% were women (n=22) and 37.1% were male (n=13). In *Carnation* group (n=35), 74.3% were female (n=26) and 25.7% were men (n=9). In the placebo group (n=35), 57.15% were female (n=20) and 42.85% were male (n=15) (P>0.05) (Table 1).

Table 1: Comparison of mean in WOMAC questionnaire index in 3 groups under study

Variables		Placebo group	Carnation group	Diclofenac group	P-value
		Mean \pm SD	Mean \pm SD	Mean \pm SD	
First examination	General pain severity	12.5 \pm 2.4	12 \pm 4.37	12.11 \pm 2.7	0.79
	Knee pain	4.11 \pm 2.01	5.01 \pm 1.9	4.82 \pm 1.6	0.076
	Morning stiffness	2.6 \pm 0.9	2.34 \pm 1.08	2.17 \pm 1.01	0.119
	Stiffness in sitting	2.42 \pm 0.75	2.17 \pm 0.95	2 \pm 0.9	0.116
Second examination	Physical performance	41.42 \pm 7.9	38.22 \pm 12.08	40.7 \pm 7.5	0.329
	General pain severity	12.5 \pm 2.6	10.7 \pm 4.5	11.45 \pm 2.7	0.09
	Knee pain	3.8 \pm 1.1	4.6 \pm 1.55	4.5 \pm 1.57	0.045
	Morning stiffness	2.34 \pm 0.8	2.2 \pm 1.64	2 \pm 1	0.49
Third examination	Stiffness in sitting	2.14 \pm 0.77	1.88 \pm 1	1.85 \pm 1	0.34
	Physical performance	41.14 \pm 7.6	34.8 \pm 12	37.6 \pm 7.01	0.017
	General pain severity	12.11 \pm 3.16	9.71 \pm 5.25	9.17 \pm 3.25	0.006
	Knee pain	3.37 \pm 1.45	3.8 \pm 1.8	3.42 \pm 1.26	0.438
Fourth examination	Morning stiffness	2.22 \pm 1.08	1.71 \pm 0.92	1.57 \pm 0.94	0.017
	Stiffness in sitting	2.05 \pm 0.93	1.7 \pm 1	1.34 \pm 0.83	0.009
	Physical performance	40.3 \pm 8.1	32.5 \pm 13.6	30.9 \pm 8.4	0.002
	General pain severity	12.25 \pm 3.4	9 \pm 5.9	7.77 \pm 3.63	0.005
Fourth examination	Knee pain	3.6 \pm 1.6	3.82 \pm 2.05	2.74 \pm 1.2	0.017
	Morning stiffness	2.34 \pm 1.23	1.74 \pm 1.03	1.22 \pm 1	0.009
	Stiffness in sitting	1.9 \pm 1.2	1.48 \pm 1.1	0.91 \pm 0.83	0.001
	Physical performance	40 \pm 8.6	30.25 \pm 14.6	26 \pm 10	0.001

In diclofenac, *Eugenia caryophyllata*, and placebo group, 45.7%, 57.1% and 51.4% of patients were in the age group between 50 and 60 years respectively. In diclofenac, *Eugenia caryophyllata*, and placebo group,

37.1%, 22.9% and 34.2% of patients were employed respectively.

The majority of patients in 3 groups were the undergraduate and married individuals (Table 2).

Table 2: Frequency distribution of demographic variables of patients in 3 groups (Q-square test)

Variables		Groups	Placebo n(%)	Carnation n(%)	Diclofenac n(%)	P-value
Age	30-40 years		4(11.4)	3(8.6)	5(14.3)	0.54
	40-50 years		3(37.15)	12(34.2)	14(40)	
	50-60 years		18(51.4)	20(57.1)	16(45.7)	
Sex	Female		20(57.15)	26(74.3)	22(62.9)	0.62
	Male		15(42.85)	9(25.7)	13(37.1)	
Job	Employed		12(34.20)	8(22.9)	13(37.1)	0.43
	Labor		6(17.1)	5(14.3)	7(20)	
	Self employed		6(17.1)	6(17.1)	7(20)	
Education	Others		11(35.2)	16(45.1)	8(22.9)	0.88
	Undergraduate		13(37.15)	14(40)	14(40)	
	Diploma		13(37.15)	12(34.2)	10(28.6)	
Marital status	Graduate		9(25.7)	9(25.7)	11(31.4)	0.63
	Single		6(17.1)	5(14.3)	8(22.9)	
	Married		29(82.9)	30(85.7)	27(77.1)	

According to results of the Q-square test, no significant difference was observed between the two groups based on age, sex and body mass index (BMI) in subjects ($P>0.05$).

Based on analysis of variance test, the mean of WOMAC questionnaire showed no significant difference (general pain severity, knee pain, morning stiffness, stiffness in sitting, sleeping, resting and physical performance) on the first examination or before treatment in group 3 ($P>0.05$).

At the second visit or one week after initiation of treatment, physical performance was significant in *Eugenia caryophyllata* group between diclofenac and placebo groups ($P=0.017$) and there was no significant difference in group 3 as the other cases (general pain, knee pain, morning stiffness, stiffness sitting, sleeping and resting) ($P>0.05$).

In the third examination or 3 weeks after initiation of treatment, general pain severity, morning stiffness, stiffness in sitting and sleeping in diclofenac group was significantly lower than in those of two other groups ($P<0.05$).

In addition, in the fourth examination or 4 weeks after initiation of treatment, general pain severity, knee pain, morning stiffness, stiffness in sitting and sleeping manners in diclofenac group was significantly lower than those which were reported in the two groups ($P<0.01$).

According to ANOVA, repeated observations and comparison in the 3 groups during the first to fourth examination, generally, mean score of WOMAC questionnaire (general pain, knee pain, morning stiffness, stiffness in sitting and sleeping and resting and physical performance) in all 3 groups (diclofenac, *Eugenia caryophyllata* and placebo) decreased significantly during the first to fourth examination ($P<0.001$).

DISCUSSION

In this study, the effect of topical ointment of *Carnation* comparing to diclofenac ointment group, a nonsteroidal anti-inflammatory drug (NSAID), and placebo group on reducing symptoms of primary knee osteoarthritis was examined. The results indicate that general pain severity of the patient was reduced significantly in the third and fourth weeks of the study.

Decrease in pain was in both diclofenac and *Eugenia caryophyllata* groups. However, this pain reduction was more significant in the group receiving topical diclofenac and it was not significant placebo group.

Besides, in the case of knee pain, it was significantly reduced in the first and fourth weeks that this pain reduction was observed in both diclofenac and *Eugenia caryophyllata* groups that decrease in knee pain was more remarkable in diclofenac ointment group and no significant change was observed in the placebo group.

Given to stiffness in sitting, standing, and resting, there was a significant decrease in the third and fourth weeks that this reduction was observed in both diclofenac and *Eugenia caryophyllata* group and pain reduction was higher in diclofenac group than that of *Eugenia caryophyllata*.

Considering to the physical performance of the patients participating in this study, physical activity increased in both diclofenac and *Eugenia caryophyllata* groups, but this increase in physical activity was more remarkable in diclofenac group.

Analgesic and anti-inflammatory effects of *Carnation* was confirmed in vitro and on animals studies several years ago. Many studies have been conducted on the properties of *Carnation*.

In a study, the effects of carbamazepine and diclofenac and placebo in

osteoarthritis knee pain relief was compared and it was shown that regarding to the comparison of the effect of carbamazepine and diclofenac in pain relief, the severity of pain reduced to the same proportion and there was no significant difference¹⁵ that this is in line with our findings. In addition, in another study that has been carried out in Shahrekord University of Medical Sciences on analgesic effect of *Eugenia caryophyllata* through intrathecal injection upon mice. It is suggested that the depth and duration of analgesia was dose-dependent and 10 min after administration of eugenol, the analgesic effect was started and 30 minutes after administration, maximum analgesic effect was observed.¹⁶

Besides, in another study that has been done in Shahid Bahonar University of Kerman on analgesic properties of eugenol (main component of carnation), analgesic effect of *Eugenia caryophyllata* has been demonstrated using formalin test on rats.¹⁷

Many studies have been done on the effects of herbal medicines to reduce the pain of knee osteoarthritis compared with NSAID drugs. However, a few studies have been conducted on the effect of carnation upon knee osteoarthritis.¹⁸

CONCLUSION

Regarding to the determination of the effect of Carnation plant extract comparing to topical diclofenac upon reducing pain, morning stiffness and stiffness during the daily activities and its impact on improving physical performance of patients in this study, it is shown that carnation was effective in the decrease of general pain, morning stiffness, knee stiffness and improvement of physical performance but the effect was not as diclofenac ointment.

Thus, it is suggested that this drug is used as an adjunctive therapy in cases that

NSAID is used to reduce the dosage and NSAID's side effects.

CONFLICT OF INTEREST

Authors have declared that no conflicts of interest exist.

ACKNOWLEDGMENT

This study is the result of grant no. 1335. IRCT code of this clinical trial study is IRCT201501056480N8. Hereby, we thanks to Deputy of Research and Technology of Shahrekord University of Medical Sciences for their financial support. We also appreciate the help of all those who cooperate with us in the fulfillment of this research.

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How to cite the article: Dehghan M, Karimi Shervedani E. Comparison of effect of topical application of *Eugenia caryophyllata* extract and topical diclofenac in primary knee osteoarthritis: a clinical trial study. *Adv Herb Med.* 2015; 1(4): 28-34.