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To compare the effect of a formulation containing Boswellia Serrata extract on the Osteoarthritis patients' pain alleviation and quality of life improvement With Placebo and Piroxicam Gel; A Randomized Double blind trial

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Abstract

Introduction: Osteoarthritis is one of the most common causes of chronic pain in an aging population, and controlling it is a must. Several methods are tried and tested every year. Osteoarthritis has an inflammatory element. Boswellia Serrata has many known Anti-Inflammatory properties. The goal of this study is to compare the effect of a formulation containing Boswellia Serrata extract on the Osteoarthritis patients' pain alleviation and quality of life improvement with Placebo and Piroxicam Gel. Methods & Materials: 60 patients were gathered in three groups in a Randomized double blinded randomized trial. The study went on for 1 month and each patient was visited by a rheumatologist at inception, days 5, 15 and 30. Routine checkups were done at each visit and patients with known medical conditions were excluded. At the start and at the end of the study liver function tests were taken. The results were then compared with each other and previous visits. Results: Piroxicam was a suitable choice for patients even in short term. It had an acceptable efficacy in improving patient's pain and improving functions, while Boswellia Serrata Extract did not cause statistically significant difference, except in Visual Analog Scale. While placebo caused some improvement in patients, it could be a result of patients' overall low level of education.

Key words: Osteoarthritis, pain, Boswellia Serrata, Piroxicam.

Introduction

Osteoarthritis (OA) is a chronic systemic disease involving the joints - mostly the knees, hands and / or the hip. The disease is usually progressive and turns into a painful problem after several years. (Hiligsmann et al., 2013) Depending on the cause, the disease is divided into primary and secondary OA. OA is the cause of pain, disability, and heavy socio-economic costs all over the world. The epidemiology of the disease is complex and multifactorial, where genetic, biological, and biomechanical causes are involved. (Glyn-Jones et al., 2015) OA is the commonest joint disease worldwide that affects 9.6% of men and 18% of women over 60 years of age. It is predicted that increase in life expectancy and aging populations turn OA to the fourth cause of disability by 2020. (Woolf and Pfleger, 2003) OA imposes a lot of costs to the economy. The figure is estimated to be about $ 89.1 billion in America. (Leigh et al., 2001)

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Moreover, it is estimated that $ 3.4 to $ 13.2 billion is spent only on job-related OA annually, which is more than the cost for asthma and pulmonary diseases, and more than the total cost of neurological and renal diseases. (Leigh et al., 2001) In developing countries, this figure can account for 1 to 2.5% of gross national product. (Hiligsmann et al., 2013) About fifty-one percent of the cost for OA is the cost directly spent on medication. Clinical diagnosis of OA is only possible when the patient is symptomatic and all medical interventions intend to prevent or remove these symptoms. Many interventions have been examined and compared concerning OA to date, but given the heavy costs for these interventions, it seems that the effort to find a cost-effective solution is good and reasonable. Among all the interventions conducted and studied, studies on medicinal plants and herbal medicines are strongly underway given their fewer adverse effects, effects comparable to other drug groups, such as corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs), as well as different mechanism of the effect of these drugs. Among these drugs, Boswellia Serrata has attracted more attention in the light of boswellic acids, especially acetyl-11-keto-beta-boswellic acid (AKBA). There are various criteria to measure the severity of the symptoms, disability, and pain in the patient. Osteoarthritis Research Society International (OARSI) and Outcome Measurement in Rheumatology (OMERACT) recommend using both self-expression criteria by the patient and functional outcomes, and accept both criteria types. However, they still have not introduced any as a gold standard.[1] The criterion introduced by Western Ontario and McMaster universities, called Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is one of these criteria[2] whose in validity, reliability, and repeatability have been approved in many studies. (McConnell et al., 2001; Basaran et al., 2010; Salaffi et al., 2003) Moreover, the Persian version of this criterion exists as well, on which many studies have been conducted confirming the reliability, validity and the repeatability of the test. (Ebrahimzadeh et al., 2014; Nadrian et al., 2012) Treating OA is divided into two categories - non-pharmacological and pharmacological ones. The first group includes patient training, exercises, using assisting tools, weight loss and using food supplements, and the second group involves simple painkillers, painkillers with opium and NSAIDs. Orthopedic surgery is for patients who have not responded to drug therapy and suffer from moderate to severe pain. (American Academy of Family Physicians NJ, Lane NE, 1970) Among the studies conducted, significant studies have been done on the Boswellia Serrata extract, known as boswellia, and its benefits have proven satisfactorily. (Ammon, 2016 ;Dragos et al., 2017; Iram et al., 2017; Karlapudi et al., 2018; Sontakke et al., 2007) The proposed mechanism of action for Boswellia Serrata and the acids taken derived from it reduces the pro-inflammatory cytokines including IL-1, IL-2, IL-6, IFN-γ and TNF-α (Sontakke et al., 2007) and inhibit the production of leukotrienes by inhibiting 5-lipoxygenase enzyme (5-LO). (Brayfield, 2017) Given the explanation, we measured the effect of new formulations produced at the Medicinal Plants and Natural Products Research Center of Ahvaz Jundishapur University in improving the symptoms of patients with OA and compared these results with the patients using other treatment methods.

Material and Method

The study was a double-blind clinical trial on humans that was conducted in patients referring to Ahvaz Golestan Hospital during the years 2018 to 2019. . The pre-implementation study was approved by the University's Ethics Committee. arrival criteria include patients with OA .The study was conducted to evaluate the effect of a formulation with Boswellia Serrata extract on chronic pain of the patients with OA and to compare it with commercial piroxicam gel and placebo. After getting the necessary permissions for the study, the formulation containing Boswellia Serrata extract was prepared and packaged as topical gel by Medicinal Plants and Natural Products Research Center of Ahvaz Jundishapur University. Then the available 0.5% piroxicam gel was commercially prepared. The gel had been prepared and manufactured by Razak Pharmaceuticals Company at razak-labs.ir. In the next stage, the placebo was prepared and packaged as a topical gel by Medicinal Plants and Natural Products Research Center of Ahvaz Jundishapur University. All packages were indistinguishable from each other with no apparent differences. All gel packets were randomly encoded and each was assigned a number from one to sixty (in three groups of twenty). Then the drug packs were delivered to the clinical study team without the encoding key. Data were analyzed by version 22, SPSS software and parametric tests were used for normal data and nonparametric tests were used for abnormal data. The meaning has described with P-value less than 0.05.

Result

Overall 60 eligible patients were enrolled in three groups (each group 20 patients), of whom 34 (56.6%) were females and 26 (43.4%) males and 57 managed to continue the study to the end. Three patients were excluded from the study given the errors in the presentation of information. From the remaining 54 patients, 17 patients were in the placebo group, 20 in the piroxicam gel group, and 17 in the group receiving the formulations containing boswellia. The mean age of the patients was 25.56 years. The youngest patient was 29 years old and the oldest 83. The mean age was 70.55 years in the placebo group, 85.56 years in the piroxicam group and 55.56 in the Boswellia Serrata formulation group, which was not statistically significant. Twenty-eight (52%) patients had primary years education, 16 (30%) had primary and high school diploma, 8 had entered university, and two had not answered the questions about their education. During the study, the patients were called 71 times to be reminded of attending and filling in the forms.Among the patients enrolled in the study, 12 (20%) patients had been admitted with right knee complaints, 8 (13%) patients left knee, and 40 (67%) patients both knees.During the study, the questionnaires of different treatment groups were compared at the starting point of the study and there was no significant difference

[1] Oarsi. Physical Performance Measures | Osteoarthritis Research Society International (OARSI).
[2] Western Ontario U, McMaster U. WOMAC - AUSCAN - Osteoarthritis Global Index.

Table 1: Patient characterizations in two groups for several assessment and grading

ANOVA[a]						
		Sum of Squares	**df**	**Mean Square**	**F**	**Sig. (p-value)**
score_sym_stif	**Between Groups**	678.990	2	339.495	.805	**.452**
	Within Groups	21922.123	52	421.579		
	Total	22601.113	54			
score_pain	**Between Groups**	2557.862	2	1278.931	2.663	**.079**
	Within Groups	24976.370	52	480.315		
	Total	27534.231	54			
score_func	**Between Groups**	2752.699	2	1376.349	2.340	**.106**
	Within Groups	30581.447	52	588.105		
	Total	33334.146	54			
score_Varzesh	**Between Groups**	2135.648	2	1067.824	1.690	**.195**
	Within Groups	32223.611	51	631.836		
	Total	34359.259	53			
score_koos	**Between Groups**	1799.786	2	899.893	2.171	**.125**
	Within Groups	20720.851	50	414.417		
	Total	22520.637	52			
Vas	**Between Groups**	1191.231	2	595.616	1.006	**.373**
	Within Groups	29604.882	50	592.098		
	Total	30796.113	52			
a. before intervention						

The results of analysis of variance (ANOVA) showed that the treatment groups did not have a significant difference in the indices before applying therapeutic intervention (P>0.05).Then the symptoms of each part of the questionnaire were analyzed separately.

WOMAC: Clinical signs and joint stiffness

The following results were obtained in the clinical symptoms and joint stiffness.

Table 2: Evaluation of stiffness symptoms in two groups

Parameter Estimates							
Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	**58.112**	**2.6055**	**53.006**	**63.219**	**497.469**	**1**	**.000**
[group=1]	**1.412**	**3.6932**	**-5.827**	**8.650**	**.146**	**1**	**.702**
[group=2]	**7.232**	**3.3477**	**.670**	**13.793**	**4.666**	**1**	**.031**
[group=3]	**0[a]**	**.**	**.**	**.**	**.**	**.**	**.**
(Scale)	**423.925**						

The results showed that after a month of study, the mean scores of clinical and stiffness symptoms improved by 7.23 units on average in the piroxicam-treated group compared to the placebo-treated group, which was statistically significant (P = 0.031). Although at the end of the study, the effect of Boswellia Serrata extract exceeded the placebo and got closer to boswellia, this distance did not reach a statistically significant level.

Pain : Comparing the pain score between the groups during the visits, the mean pain score in the piroxicam group improved 12.32 units on average compared to the placebo group, which was statistically significant (P = 0.001). Although in Boswellia Serrata group, the mean score of pain at the end of the study was about eight units higher than that of the placebo group, it was not statistically significant at 95% confidence level - however it was very close to significance (P=0.055).

Function:

The next criterion studied was the joint performance criterion. In this criterion, the piroxicam receiving group, on average, experienced 13.65 units improvement compared to the placebo group, which was statistically significant (P=0.001). The group receiving Boswellia Serrata had about 8.40 units of functional improvement, which was not statistically significant compared to the placebo group (P = 0.079).

Table 3: Evaluation of score func in two groups

Parameter Estimates							
Parameter	**B**	**Std. Error**	**95% Wald Confidence Interval**		**Hypothesis Test**		
			Lower	**Upper**	**Wald Chi-Square**	**df**	**Sig.**
(Intercept)	45.840	3.3301	39.314	52.367	189.490	1	.000
[group=1]	8.408	4.7850	-.970	17.786	3.088	1	.079
[group=2]	**13.655**	4.0702	5.678	21.632	11.255	1	**.001**
[group=3]	0[a]	.	.	.	.	.	.
(Scale)	649.919						

Dependent Variable: score_func
Model: (Intercept), group
a. Set to zero because this parameter is redundant.

Knee Injury and Osteoarthritis Outcome Score (KOOS)

All patients were asked to answer the questions of KOOS. Every component of this criterion was also examined.

Exercise and physical activities

In this section, piroxicam improved the patients' physical activity by 14.716, which was significant (P <0.001). Boswellia Serrata could increase the physical activity of patients by about 9 scores, which was not significantly different from placebo, although it was close to statistical significance (P = 0.058).

Table 4: Evaluation of score_Varzesh in two groups

Parameter Estimates							
Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	32.143	2.8919	26.475	37.811	123.540	1	.000
[group=1]	8.906	4.6983	-.303	18.114	3.593	1	.058
[group=2]	**14.716**	4.0203	6.836	22.596	13.399	1	**.000**
[group=3]	0[a]	.	.	.	.	.	.
(Scale)	681.840						

Dependent Variable: score_Varzesh
Model: (Intercept), group
a. Set to zero because this parameter is redundant.

Life quality connected with knee

Concerning this criterion, piroxicam improved 15.13 score compared to placebo group, which was statistically significant (P<0.001).In the group receiving boswellia, the improvement was 6.373, which did not approach statistical significance (P = 0.125).

Table 5: Evaluation of score_koos in two groups

Parameter Estimates							
Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	39.221	2.6744	33.979	44.463	215.068	1	.000
[group=1]	6.373	4.1594	-1.779	14.526	2.348	1	.125
[group=2]	**15.130**	3.3635	8.538	21.723	20.236	1	**.000**
[group=3]	0[a]	.	.	.	.	.	.
(Scale)	474.660						

Dependent Variable: score_koos
Model: (Intercept), group

a. Set to zero because this parameter is redundant.

Visual Analog Scale (VAS)

All the patients were asked to rate their pain at any time using VAS.The results obtained from this criterion are as follows.

Table 6: Evaluation of score vas in two groups

Parameter Estimates							
Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
(Intercept)	69.638	2.8091	64.132	75.143	614.567	1	.000
[group=1]	**-11.485**	4.4944	-20.294	-2.676	6.530	1	**.011**
[group=2]	**-9.856**	4.0001	-17.696	-2.016	6.070	1	**.014**
[group=3]	0[a]	.	.	.	.	.	.
(Scale)	639.196						

Dependent Variable: Vas

Model: (Intercept), group

a. Set to zero because this parameter is redundant.

The results show that the mean VAS was 9.86 times lower in the piroxicam group compared to the placebo group during treatment visits (P = 0.014).Moreover, the mean of this index in the treatment group receiving Boswellia Serrata was 11.5 units lower than placebo group, which was statistically significant (P = 0.011).

Lequesne Functional Index

This criterion includes the physician's examinations while visiting the patient, plus patient responses to some questions. In each visit, the relevant criteria were measured by the expert physician, but the patient response rate to the questions related to this criterion was far less than acceptable (38%). Thus, the results obtained from this criterion were not included in data analysis.

Using rescue medication: Patients reported using rescue medications 58 times in 216 visits. This use was 11 times in the piroxicam group, 34 times in the placebo group and 13 times in the Boswellia Serrata group.

Complications: No complications were reported during the study.

Discussion

Our study was a double-blind study to measure the effect of a formulation containing Boswellia Serrata. Many studies had been conducted on Boswellia Serrata extracts (in combination with other materials or alone). Most of these studies had reported conflicts of interest. In this study, the formulation was developed by our research center and studied to do away with any possibility of interest conflict. The study had some limitations. A flood occurred at the study site during the study, whose effect on the patients' use of drugs and visiting the treatment center is uncertain. Moreover, financial constraints prevented a longer study. Patients in the placebo group reported a high response rate to placebo in most cases, reducing our certainty and confidence in the results. All previous studies had used oral medication for comparison. Our study first compared topical drugs to compare the effect of three times daily doses of piroxicam gel with Boswellia Serrata extract and placebo extract on pain in patients with OA. We used 0.5% piroxicam gel produced by Razak lab. Piroxicam is a NSAID used to relieve symptoms of painful inflammations like arthritis. The piroxicam mechanism of action is by inhibiting endogenous prostaglandins in biological pathways related to pain, stiffness, tenderness and swelling and is commonly used to treat problems like rheumatoid arthritis and OA, dysmenorrhea, and postoperative pain. This medicine is used as pills, capsules and gels (0.5%). (Brayfield, 2017) Piroxicam has also been studied in several studies as a good alternative for controlling pain in patients with short-term (Heynen and Dessain, 1983) and long-term OA. (Zizic et al., 1985) Many studies have shown that the performance of NSAIDs for controlling chronic pain is comparable to or equal to oral NSAIDs, and these drugs also have less digestive adverse effects compared to their oral substitutes. (Klinge and Sawyer, 2013 ;Heyneman et al., 2000) Our study showed that 0.5% piroxicam gel is an appropriate option in one month to control pain in patients with OA and can improve the pain score 13 times on average in WOMAC scale and about 9 in VAS scale, which was statistically significant. This result was consistent with the previous studies of the usefulness of NSAIDs in controlling OA pain. (Huskisson, 1983) In Heynen and Dessain studies similar results were reported in 2-4 weeks using piroxicam suppository in patients with OA and rheumatoid arthritis .Boswellia Serrata extract was used as a topical ointment for rubbing on the spot for the first time in our study. Previously, many studies (Sontakke et al., 2007; Kimmatkar et al., 2003; Sengupta et al., 2008; Sengupta et al., 2010; Vishal et al., 2011) had used this substance (combined with other materials or individually) orally to improve pain in OA. Our study used Boswellia Serrata extract alone for this purpose for the first time. Boswellia Serrata extract significantly reduced the patients' pain in the VAS index, which was statistically significant. Although in other indices, it approached significance (exercise and physical activities of KOOS, as well as pain and function in WOMAC) it did not reach the acceptable level for this study. In our study, the response rate to placebo was high. Although ultimately piroxicam was significantly more effective than placebo, placebo had

significant effects on cases requiring filling the questionnaire. This can be attributed to the fact that the average age of participants was high (56.25) and their level of education was relatively low in our study. This can justify the fact that the result of our study varies in WOMAC and VAS criteria: in the first pain criterion, the result was insignificant but not in the second.

Conclusion

In the short term, piroxicam as a 0.5% topical gel can significantly better clinical symptoms and stiffness, pain, daily performance and activities, exercise and physical activity, life quality, as well as the mean score of pain in VAS. This drug can have this effect in just a short period, like 4 weeks. Piroxicam showed a better performance than Boswellia Serrata extract and placebo. Although in many studied factors Boswellia Serrata extract as a topical gel approached statistical significance, there were no statistically significant differences except for the improvement of pain in VAS scale. Although these results are still significant and cannot nullify the efficiency of Boswellia Serrata extract as pain relief for patients with OA, it did not show the required effect at the expected significant level in the studied population and produced thus.

Suggestions

In similar studies, one can define the inclusion criteria in a way that people with higher levels of educations are included. According to similar studies, one can use Boswellia Serrata gel as an adjunct to other drugs and measure its effect.As towards the end of the study, the effect of Boswellia Serrata extract was increasing in some factors nearer and it was possible that this increase would continue if the study continued, it is recommended that longer studies be conducted in this regard.

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