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Original Research

Evaluation of safety and tolerability of Rosehip extract in treatment of knee osteoarthritis patients

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ABSTRACT:

Background – OA has high prevalence, especially in the elderly and high rate of disability related to disease makes it a leading cause of morbidity in the elderly. Symptoms in OA include joint pain, stiffness, decreased range of motion etc. Pharmacological treatment is mostly palliative. Rose hip has shown promising results in reducing pain, stiffness and disability in various studies mostly done in scandinavia. The rose hip (or rose haw) is the pseudo fruit of the rose plant. **Aim and objectives-** To check laboratory parameters and the safety of rosehip extract in patients with osteoarthritis of knee. **Materials and methods-** Osteoarthritis of knee joint diagnosed according to clinical and radiological criteria of American College of Rheumatlogy (ACR), controlled uncomplicated co-morbid conditions were included in the study while, inflammatory arthritis, traumatic osteoarthritis, ligament injury, severe OA with deformity, fibromyalgia, depression, substantial abnormalities in haematological, hepatic, renal or metabolic functions, Patients who received glucosamine sulphate, chondroitin sulphate, intra-articular hyaluronate, systemic or intra-articular glucocorticoids in 6 weeks preceding enrolment, history of drug or alcohol abuse, cancer, pregnancy and lactation were excluded in the study. **Results-** Mean Erythrocyte sedimentation rate (ESR) value got reduced in patients of both the groups ($p<0.001$). ESR decreased from 22.71 ± 6.44 at 0 week to 20.05 ± 4.60 at 12 weeks in Group 1, while it decreased from 21.92 ± 7.6 at 0 week to 20.42 ± 6.97 at 12 weeks in Group 2. Reduction in mean ESR levels was observed to be comparable in both the groups ($p> 0.05$). Both the groups were comparable as far as safety is concerned and ADR's reported didn't require any discontinuation of therapy. **Conclusion-** The results of our current study are very encouraging in favour of market preparation of rose hip extract as an adjuvant in treatment of osteoarthritis as it leads to no additional safety concerns. However the findings of current study need to be substantiated by larger randomized, placebo-controlled clinical trials.

Keywords- Articular cartilage, Subchondral bone, Alkaline Phosphatase, Lactate Dehydrogenase

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INTRODUCTION

Osteoarthritis (OA) is a disease characterized by degeneration of cartilage and underlying bone within a joint and is accompanied by bony overgrowth. The breakdown of these tissues eventually leads to pain and joint stiffness. Knees are the most commonly affected joints. Disease onset is gradual and usually begins after the age of 40 years.[1] OA is one of the most prevalent and disabling chronic joint diseases in humans. It is a degenerative disease resulting from a group of mechanical abnormalities involving joints, articular cartilage and subchondral bone. Osteoarthritis is derived from greek words "osteo" meaning the bone, "ortho" meaning joints and "itis" which means inflammation. Its high prevalence, especially in the elderly and high rate of disability related to disease makes it a leading cause of morbidity in the elderly. Symptoms in OA include joint pain, stiffness, decreased range of motion etc.[2] Pharmacological treatment is mostly palliative. Rose hip has shown promising results in reducing pain, stiffness and disability in various studies mostly done in scandinavia.[3] The rose hip (or rose haw) is the pseudo fruit of the rose plant. A study was done on 13

healthy volunteers, each treated with 45 g of rose hip powder daily for 4 weeks, followed by at least 1 month of withdrawal and further treatment with 10 g rose hip powder daily for a final 4-week period. The rose hip preparation used was based on the natural amount of seeds and shells from a subspecies of *r.* Canina (lito).[4] There was a significant decline in crp as the result of 4-week treatment with the high dose of rose hip powder, and this finding was supported by a decline in the chemotaxis of polymorphonucleated leucocytes (pmns).[5] There were no changes in potassium, sodium, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, bilirubin, or hemoglobin levels in the test subjects, indicating that the powder was well tolerated.[6]

Rosehip extract has the potential to revolutionize the treatment of Osteoarthritis but safety needs to be properly established. As studies on its role and safety are limited especially in our set up, we aimed to conduct a study to check the laboratory parameters and safety of rosehip extract in knee osteoarthritis.

MATERIALS AND METHODS

A prospective, randomized, open-label, placebo-controlled add-on clinical trial was conducted in the Postgraduate Department of Pharmacology and Therapeutics in collaboration with Postgraduate Department of Orthopedics and Department of Ayush at Government Medical College, Jammu for a period of one year starting from 2016. The study protocol was approved by the Institutional Ethics Committee, Government Medical College, Jammu vide no. IEC/Thesis/Research/T13B/2016/294 dated 7/10/2017 and also by the Institutional Review Board, GMC Jammu. Study participants were taken from the patients attending Orthopaedics Outpatient Department diagnosed with osteoarthritis of knee. Written informed consent was obtained from the patients after explaining them the nature and purpose of the study. Patients with age over 40 years, both male and female patients, Osteoarthritis of knee joint diagnosed according to clinical and radiological criteria of American College of Rheumatlogy (ACR), controlled uncomplicated co-morbid conditions were included in the study while, inflammatory arthritis, traumatic osteoarthritis, ligament injury, severe OA with deformity, fibromyalgia, depression, substantial abnormalities in haematological, hepatic, renal or metabolic functions, Patients who received glucosamine sulphate, chondroitin sulphate, intra-articular hyaluronate, systemic or intra-articular glucocorticoids in 6 weeks preceding enrolment, history of drug or alcohol abuse, cancer, pregnancy and lactation were excluded in the study.

The patients were then randomized into two groups:

Group 1: Comprised of patients who were put on Rose hip extract 750 mg 2 capsules twice a day orally for 3 months as an add-on therapy to tablet Paracetamol 650 mg BD.

Group 2: Comprised of patients who were put on placebo orally for 3 months as an add-on therapy to tablet Paracetamol 650 mg BD.

Standard treatment was given in both the groups according to ACR 2012 recommendations and the patients were assessed at subsequent follow-up visits at 4 weeks, 8 weeks and 12 weeks for following safety parameters. The safety profile of the drugs was studied and compared on the basis of adverse drug reactions which were documented in ADR reporting forms by the Central Drug Standard Control Organization. The data was analyzed with the help of SPSS version 20.0 for windows. Baseline comparability was assessed by using chi square/ t test as deemed appropriate. Mean and SD was calculated and statistical significance evaluated using repeated measures ANOVA. Post hoc Bonferroni correction was used to measure statistical significance intragroup. A p value of 0.05 was considered as statistically significant.

RESULTS

The study enrolled 75 patients in the age group of 40 years or more (mean ± standard deviation, 51.44 ± 7.57 years) of either sex, diagnosed with mild to moderate osteoarthritis of knee according to clinical and radiological criteria of American College of Rheumatology. Patients were assessed at subsequent follow-up visits at 4, 8 and 12 weeks for efficacy and safety parameters. No patient was lost to follow-up. The patients were randomized into two groups – Group 1 (n=35) comprised of patients who were put on Rose hip extract 1.5g twice a day orally for 3 months as an add on therapy to the standard treatment and Group 2 (n=40) comprised of patients who were put on placebo twice a day orally for 3 months as an add on therapy to the standard treatment.

Table 1. Distribution of Patients According to Age

Age Group (in years)	Group 1 (n=35) No. (%)	Group 2 (n=40) No. (%)
40 – 49	11 (31.43)	19 (47.50)
50 – 59	18 (51.43)	16 (40.00)
60 – 69	6 (17.14)	5 (12.50)
Total	**35**	**40**
Mean Age ± Standard Deviation (Range)	**52.8 ± 7.33 (40 – 68) years**	**50.25 ± 7.66 (40 – 68) years**
Statistical Inference (Unpaired 't' test)	**t=1.46; p=0.14; Not significant**	

Table 2. Distribution of Patients According to Gender

Gender	Group 1 (n=35) No. (%)	Group 2 (n=40) No. (%)	Statistical inference (Fisher's exact test)
Male	10 (28.57)	12 (30.00)	**p=1.00; Not significant**
Female	25 (71.43)	28 (70.00)	
Total	**35**	**40**	
Male to Female Ratio	**1:2.5**	**1:2.33**	

Table 3. Comparison of Mean Weight of Patients

Variable	Group 1 (n=35)	Group 2 (n=40)
Mean Weight ± Standard Deviation	68.2+6.64	67.75+6.70
Range (in kg)	57-78	52-78
Statistical Inference (Unpaired 't' test)	**t=0.35; p=0.72; Not Significant**	

Table 4. Distribution of Patients According to Demographic Profile

Place of Residence	Group 1 (n=35) No. (%)	Group 2 (n=40) No. (%)	Statistical inference (Fisher's exact test)
Urban	23 (65.71)	28 (70.00)	**p=0.80; Not significant**
Rural	12 (34.29)	12 (30.00)	
Total	**35**	**40**	

Table 5. Distribution of Patients According to Knee Involved

Knee Involved	Group 1 (n=35) No. (%)	Group 2 (n=40) No. (%)	Statistical Inference (Fisher's exact test)
Bilateral	20 (57.14)	19 (47.50)	**p=0.48; Not significant**
Right	9 (25.72)	11 (27.50)	
Left	6 (17.14)	10 (25.00)	
Total	**35**	**40**	

Table 6. Distribution of Patients According to Personal History

Personal History		Group 1 (n=35) No. (%)	Group 2 (n=40) No. (%)
Hypertension	Yes	5 (14.29)	1 (2.50)
	No	30 (85.71	39 (97.50)
Diabetes mellitus	Yes	1 (2.86)	2 (5.00)
	No	34 (97.14)	38 (95.00)
Smoking	Yes	1 (2.86)	2 (5.00)
	No	30 (97.14)	38 (95.00)
Alcohol consumption	Yes	0	0
	No	35 (100.00)	40 (100.00)

Age Distribution - In Group 1, maximum patients were in the age group of 50-59 years (51.43%), followed by 40-49 years (31.43%) and 60-69 years (17.14%). In Group 2, maximum patients were in the age group of 40-49 years (47.50%), followed by 50-59 years (40%) and 60-69 years (12.50%).Thus, majority patients were in the cumulative age group of 40 to 59 years in both the groups and mean age of patients in both the groups was comparable (p=0.14). (Table 1)

Gender Distribution

Female patients outnumbered male patients in both the groups. In Group 1, there were 28.57% male and 71.43% female patients. In Group 2, there were 30% male and 70% female patients. Male to female ratio in Group 1 was 1:2.5 and in Group 2 was 1:2.33. Distribution was comparable in both the groups (p=1.00) (Table 2).

Weight Distribution

Mean weight ± standard deviation in Group 1 was 68.2 ± 6.64 with range of 57 to 78 kg and that of Group 2 was 67.65 ± 6.70 with range of 52 to 78 kg. The difference in mean weight between the two groups was not significant (p=0.72). (Table 3).

Demographic Profile
Patients were equally distributed according to place of residence in both the groups (p=0.80). In Group 1, there were 65.71% patients residing in urban areas and 34.29% in rural areas. In Group 2, there were 70% patients residing in urban areas and 30% in rural areas. (Table 4).

Joint involvement
In Group 1, maximum patients had osteoarthritis of both knees (57.14%), followed by right knee (25.72%) and left knee (17.14%). Similarly in Group 2, maximum patients had osteoarthritis of both knees (47.50%), followed by right knee (27.50%) and left knee (25%). The difference between the two groups was not significant (p=0.48). (Table 5).

Personal history
History of hypertension was present in five (14.29%) patients in Group 1 and one patient (2.50%) in Group 2. Diabetes mellitus was present in one (2.86%) patient in Group 1 and two patients (5%) in Group 2. Smoking history was present in one patient (2.86%) patient in Group 1 and two patients (5%) in Group 2. No patient in either of the group consumed alcohol. (Table 6).

Laboratory Parameters
Patients were evaluated for inflammatory markers like C Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR)

Table 7- Distribution of Patients According to C Reactive Protein

C Reactive Protein (CRP)		Group 1 (n=35) No. (%)	Group 2 (n=40) No. (%)
Week 0	Negative	32 (91.43)	39 (97.50)
	Positive	3 (8.57)	1 (2.50)
Week 12	Negative	35 (100.00)	40 (100.00)
	Positive	0	0

In Group 1, three (8.57%) patients and in Group 2, one (2.50%) patient had positive CRP at week 0. By week 12, the CRP levels were normal in these patients in both the groups(table-7)

Table 8 Inter Group Comparison of Mean Erythrocyte Sedimentation Rate at 0 and 12 Weeks Between Group 1 and Group 2

Erythrocyte Sedimentation Rate			
Time (in weeks)	Group 1 (n=35) Mean ± SD	Group 2 (n=40) Mean ± SD	Statistical Inference (t-test)
0	22.71 ± 6.44	21.92 ± 7.65	t=0.47; p=0.63; NS*
12	20.05 ± 4.60	20.42 ± 6.97	t=-0.26; p=0.79; NS*

NS* – Not Significant

ESR Values
Mean Erythrocyte sedimentation rate (ESR) value got reduced in patients of both the groups (p<0.001). ESR decreased from 22.71 ± 6.44 at 0 week to 20.05 ± 4.60 at 12 weeks in Group 1, while it decreased from 21.92 ± 7.6 at 0 week to 20.42 ± 6.97 at 12 weeks in Group 2. Reduction in mean ESR levels was observed to be comparable in both the groups (p> 0.05) (Table 8).

Table 9. Group Comparison of Adverse Drug Reaction

ADR	Group 1 (n=35) Mean ± SD	Group 2 (n=40) Mean ± SD
Gastritis	1	2
Diarrhoea	1	0
Vomiting	0	1
Nausea	0	1

Causality Assessment : Possible
Severity : Ranging from mild to moderate

There were a total of two adverse drug reactions (ADR's) in Group 1 and four in Group 2. In Group, one patient had diarrhea and one had gastritis. In Group 2, two patients had gastritis, one patient had vomiting and one patient had nausea. There was no significant difference between the two groups (p>0.05) .The casuality assessment of all the ADR's was carried, which was possible and was also comparable. Further, all the ADR's were mild to moderate in nature and none of the reactions was serious warranting withdrawl or change of treatment.(Table-9)

DISCUSSION

OA is described as the disease of old. With age, joints become vulnerable for OA. The body's ability to repair cartilage deteriorates with increasing age as the osteoarthritic cartilage is chemically different from normal cartilage of the same age. As chondrocytes age, they lose their ability to make repairs and produce more cartilage. This process plays an important role in the development and progression of OA. In the present study average weight among patients of Group A was 68.2 ± 6.64, while in Group B it was 67.65 ± 6.70. These finding are similar to an study.[7] The body weight of patients was between 60.52± 10.49 to 61.48± 9.04 in the first study; whereas the weight of the patients in the second study was between 66.8±14.0 to 68.0± 13.9. The association between the Body Mass Index (BMI) and knee OA is of great importance, since knee OA has strong correlation with the highly inflammatory metabolic environment found in obesity. Cytokines associated to the adipose tissue i.e adiponectine, leptine and resistine, can influence OA through the direct degradation of the articular cartilage or by controlling local inflammatory processes. Obesity increases mechanical stress on joints whereas weight loss reduces the pain and improves the physical function of the OA patients.[8]

In present study females were found to be more affected with male: female ratio of 1: 2.5. Similar findings were reported by number of authors showing higher occurrence of OA among females ranging between 52 to 87%.[9] Higher prevalence of OA in females is because of hormonal factors affecting women during menopausal phase. Women with co-morbid osteoporosis are also at higher risk of developing OA. Demographic profile showed higher prevalence of OA in urban population than rural population. Similar results were seen in other studies where significant differences were seen in its prevalence in rural (32.6%) and urban areas (60.3%). Less prevalence among rural areas may be due to more physical work, higher tolerance, less obesity, diet and lifestyle as well as less awareness of symptoms.[9] Knee OA has been associated with physical inactivity with obesity adding to the risk. Joint cartilage breaks down often because of mechanical stress or biochemical alteration causing the bone the bone underneath to fail. Bilateral involvement of Joints in both groups was more common in current study. Results were similar to that where the prevalence of unilateral and bilateral knee OA was 12.3% and 49.5%.[10] Among unilateral OA, right joint was involved more in both groups. These findings are similar to another study as their results showed that right Knee OA was 23% more as compared to 16.3% of left side. [11]

Both the groups were also evaluated for laboratory parameters like ESR and CRP. ESR values significantly decreased in both the groups ($p<0.001$) at 12 weeks but reduction in ESR values was comparable in both the groups. CRP values also became negative in both the groups at 12 weeks. OA is thought to be an inflammatory condition associated with increase in levels of inflammatory markers like ESR and CRP and treatment provided in both the groups decreased the levels of both these which is in accordance with studies[12] in a meta-analysis found that rosehip when given for 12 weeks reduces CRP levels in patients with osteoarthritis of knee. Also no patient required any of the rescue medication during the entire duration of study. These results were similar to that found in the study wherein consumption of rescue medication reduced significantly with active treatment with rosehip as compared to placebo ($p < 0.027$). Regarding safety, both the regimes were generally well tolerated.[13] During study period, six adverse drug reactions occurred, two in Group A and four in Group B. Group 1, one patient presented with gastritis and one with diarrhoea while in Group 2, two patients reported with gastritis, one with vomiting and one with nausea. All the patients completed the study. These results were similar to a study[14] wherein they found no major side effect in both rosehip and placebo groups. In contrast to nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin, rosehip has anti-inflammatory actions that do not have ulcerogenic effects and do not inhibit platelets or influence the coagulation cascade or fibrinolysis, thereby avoiding potential side effects for patients who may be at increased risk from the gastrointestinal or cardiovascular side effects of NSAID's.[15]

CONCLUSION

Both the groups were comparable as far as safety is concerned and ADR's reported didn't require any discontinuation of therapy. The results of our current study are very encouraging in favour of market preparation of rose hip extract as an adjuvant in treatment of osteoarthritis as it leads to no additional safety concerns. However the findings of current study need to be substantiated by larger randomized placebo controlled clinical trials to reassure its safety in the long run

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