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Original Research

Assessment of Efficacy of Rosehip Extract in Treatment of patients with Osteoarthritis of Knee

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ABSTRACT:

Background- The main objectives in the management of OA are to reduce symptoms, minimize functional disability, limit the progression of structural changes and ultimately delay or avoid arthroplasty. **Aims and Objectives-** To check the efficacy and safety of rosehip extract in patients with osteoarthritis of knee. **Materials and methods-** The patients were randomized by employing randomization software. The patients reporting to Orthopaedics OPD with knee pain were screened for OA. Prior to intervention, a detailed clinical history, physical examination and baseline investigations were carried out. The selected patients with mild to moderate OA diagnosed according to ACR guidelines were enrolled for study. **Results-** More improvement in joint pain, stiffness and physical function was observed in Group 1 patients as compared to Group 2 patients ($p<0.001$) at 4, 8 and 12 weeks respectively. **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 patients of osteoarthritis of knee.

Keywords- Glucosamine, Chondroitin sulphate, Diacerin, disease modifying osteoarthritic drugs, articular cartilage.

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INTRODUCTION:

Osteoarthritis (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 which may affect any joint but primarily affected joints include cervical and lumbosacral spine, hip, knee and 1st metatarsophalangeal joint. Symptomatic knee OA is currently the fourth leading cause of disability worldwide.[1] It occurs in ~12% of persons aged >60 years in US and 6% of all adults aged > 30 years. It has gradual onset and symptoms usually do not appear until the age of 45-50 years.[2] Overall prevalence of OA in India is believed to be 17-60.6%. Its prevalence increases with age so that 11% of women over 60 years have symptoms due to knee OA [3]. Overall prevalence of knee OA in India is found to be 28.70%.[4] Prevalence is found to be more in females (31%) than males (28.7%).

Current pharmacological treatment is mostly palliative.[5] NSAIDs, acetylsalicylic acid and glucocorticoids are often used for treatment of symptoms but do not affect the underlying pathogenesis of articular diseases, thus have a minimal role in modifying disease course. Besides these can also result in serious side effects such as bleeding, gastric erosions, and liver and kidney damage.[6] NSAID's are commonly used analgesics in Osteoarthritis.[7] Paracetamol, which for a decade was regarded as a safe drug, has now been reported to enhance the risk of upper gastrointestinal problems.[8] There has been increase in the use of disease modifying osteoarthritic drugs (DMOAD) whose actions are basically aimed at preventing breakdown of articular cartilage.[9] Drugs belonging to this group are Glucosamine, Chondroitin sulphate, Diacerin but

there are conflicting reports regarding their efficacy.[10] In this context, there has been a search for new alternative compounds that could minimize pain and stiffness without the serious side effects.[11] So Rose hip, a nutraceutical, with some evidence of effectiveness shown in arthritis according to Australian Rheumatology Association might change the course of treatment in patients with OA in future. As food, rosehip is used in tea, jams, jellies and soups, and as a natural source of Vitamin C.[12] Antioxidant effect is due to high phenolic and flavonoid content and is thus responsible for protective effects against oxidative stress, enhanced activity of antioxidant enzymes such as superoxide dismutase and catalase.[13] In January 2011, the evidence for rose hip was reviewed by Arthritis Australia and for the first time rose hip was included in the Arthritis Australia Complementary medicine information sheet**.**[14]. The present trial was an endeavour to generate more robust data and to establish its clinical role.

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 efficacy and safety parameters:

A- Efficacy parameters:

WOMAC Index - Western Ontario and Mcmaster Universities Osteoarthritis

To assess pain, stiffness and physical function in patients with hip and/or knee osteoarthritis.

- First developed in 1982 at Ontario and McMaster Universities. Since then it has gone multiple revisions. The latest version is WOMAC 3.1 which is available in over 100 alternate language forms.
- The sensitivity responsiveness and validity is well established
- Includes a validated disease specific questionnaire addressing joint pain (five questions), stiffness (two questions), limitations of physical function (17 questions) wherein each question is given points ranging from 0 to 4 with a total of 96 points
- Higher WOMAC score indicates poor results and the score is judged as excellent if it is below14, good if it is between 15 and 28, fair if it is between 29 and 38 and poor if it is above 38

Score Interpretation:

Higher scores indicated worse pain, stiffness or physical function.

[B] 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.

Statistical Analysis-

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. 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. 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.

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). 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). 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). 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. 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). 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 1a. Mean WOMAC Scores (±SD) of joint pain at 0, 4, 8, 12 Weeks analysed by Mixed Method (Repeated Measure) ANOVA

WOMAC Scores of Joint Pain			
Time (in weeks)	**Group 1 (n=35) Mean ± SD**	**Group 2 (n=40) Mean ± SD**	**Statistical Inference**
0	12.31 ± 2.19	12.85 ± 1.83	F (1.99,145.56)= 614.80; p<0.001.
4	8.65 ± 1.81	10.20 ± 1.24	
8	6.17 ± 1.67	7.95 ± 1.25	
12	3.42 ± 1.11	6.45 ± 1.33	

Mauchley's test of sphericity indicates that assumption of sphericity has been violated, Mauchley's W= .438 chi square(5)= 59.25 p<0.001. Therefore GG correction has been applied.

Table 1b. Post-hoc Intragroup Comparison Between Mean WOMAC Scores of Joint Pain at 0, 4, 8, 12 Weeks

WOMAC Scores of Joint Pain		
Time (in weeks)	**Mean Difference**	**Statistical Inference (Bonferroni)**
0 vs 4	3.15	p<0.001, HS
0 vs 8	5.52	p<0.001, HS
0 vs 12	7.64	p<0.001, HS

WOMAC Score for joint pain

More improvement in joint pain was observed in Group 1 patients as compared to that in Group 2 patients (p<0.001) (Table 1a). Post hoc tests using the Bonferroni correction revealed that mean WOMAC score of joint pain reduced by an average of 3.15 (p<0.001), 5.52 (p<0.001), 7.64 (p<0.001) points at 4, 8 and 12 weeks respectively (Table 1b). The mean differences in pain along different time periods and between groups was found to be statistically significant (p< 0.001).

Table 2a. Mean WOMAC Scores (±SD) of stiffness at 0, 4, 8, 12 Weeks analysed by Mixed Method (Repeated Measure) ANOVA

WOMAC Scores of Stiffness			
Time (in weeks)	**Group 1 (n=35) Mean ± SD**	**Group 2 (n=40) Mean ± SD**	**Statistical Inference**
0	3.97 ± 0.98	4.35 ± 0.66	F(2.44, 178.17)= 386.20; p<0.001.
4	2.62 ± 0.97	3.40 ± 0.74	
8	1.57 ± 0.65	2.90 ± 0.70	
12	0.51 ± 0.65	2.20 ± 0.68	

Mauchley's Test of sphericity indicates that assumption of sphericity has been violated, Mauchley's W=.722 chi square(5)= 23.363 p=<0.001. Therefore GG correction has been applied.

Table 2b. Post-hoc Intragroup Comparison Between Mean WOMAC Scores of Stiffness at 0, 4, 8, 12 Weeks

WOMAC Scores of Stiffness		
Time (in weeks)	**Mean Difference**	**Statistical Inference (Bonferroni)**
0 vs 4	1.14	p<0.001, HS
0 vs 8	1.92	p<0.001, HS
0 vs 12	2.80	p<0.001, HS

WOMAC Score for stiffness

More improvement in stiffness was observed in Group 1 patients as compared to that in Group 2 patients (p<0.001) (Table 2a). Post hoc tests using the Bonferroni correction revealed that mean WOMAC score of stiffness reduced by an average of 1.14 (p<.001), 1.92 (p<.001), 2.80 (p<.001) points at 4, 8 and 12 weeks respectively (Table 2b).The mean differences in stiffness along different time periods and between groups was found to be statistically significant (p<0.001).

Table 3a. Mean WOMAC Scores (±SD) of physical function at 0, 4, 8, 12 Weeks analysed by Mixed Method (Repeated Measure) ANOVA

WOMAC Scores of Physical Functions			
Time (in weeks)	**Group 1 (n=35) Mean ± SD**	**Group 2 (n=40) Mean ± SD**	**Statistical Inference**
0	37.62 ± 4.83	42.70 ± 6.07	F (2.00, 146.64)= 867.95; p<0.001.
4	26.42 ± 4.25	35.47 ± 6.44	
8	17.14 ± 3.96	27.50 ± 5.98	
12	8.97 ± 2.62	19.30 ± 6.14	

Mauchley's Test of sphericity indicates that assumption of sphericity has been violated, Mauchley's W=.487 chi square (5)= 51.58 p=<0.001. Therefore GG correction has been applied.

Table 3b. Post-hoc Intragroup Comparison Between Mean WOMAC Scores of Physical Functions at 0, 4, 8, 12 Weeks

WOMAC Scores of Physical Functions		
Time (in weeks)	**Mean Difference**	**Statistical Inference (Bonferroni)**
0 vs 4	9.21	p<0.001, HS
0 vs 8	17.84	p<0.001, HS
0 vs 12	26.02	p<0.001, HS

WOMAC Score for physical function

More improvement in physical functions was observed in Group 1 patients as compared to that in Group 2 patients (p<0.001) (Table 3a). Post hoc tests using the Bonferroni correction revealed that mean WOMAC score of physical functions reduced by an average of 9.21 (p<.001), 17.84 (p<.001), 26.02 (p<.001) points at 4, 8 and 12 weeks respectively (Table 3b). The mean differences between physical functions along different time periods and between groups was found to be statistically significant (p<0.001).

Table 4a. Mean WOMAC Scores (±SD) of total scores at 0, 4, 8, 12 Weeks analysed by Mixed Method (Repeated Measure) ANOVA

WOMAC Scores of Total Scores			
Time (in weeks)	**Group 1 (n=35) Mean ± SD**	**Group 2 (n=40) Mean ± SD**	**Statistical Inference**
0	53.74 ± 6.85	59.85 ± 6.89	F(1.79, 131.22)= 1180.61; p<0.001.
4	37.60 ± 5.96	49.07 ± 6.94	
8	24.94 ± 5.06	38.35 ± 6.87	
12	12.91 ± 3.33	28.00 ± 6.95	

Mauchley's Test of sphericity indicates that assumption of sphericity has been violated, Mauchley's W=.355 chi square(5)= 74.217 p=<.001. Therefore GG correction has been applied.

Table 4b. Post-hoc Intragroup Comparison Between Mean WOMAC Scores of Total Scores at 0, 4, 8, 12 Weeks

WOMAC Scores of Total Scores		
Time (in weeks)	**Mean Difference**	**Statistical Inference (Bonferroni)**
0 vs 4	13.45	p<0.001, HS
0 vs 8	25.15	p<0.001, HS
0 vs 12	36.33	p<0.001, HS

Total WOMAC Score

More improvement in mean total score was observed in Group 1 patients as compared to that in Group 2 patients (p<0.001) Post hoc tests using the Bonferroni correction revealed that mean total WOMAC score got reduced by an average of 13.45 (p<.001), 25.15 (p<.001), 36.33 (p<.001) points at 4, 8 and 12 weeks respectively The mean differences in total WOMAC scores along different time periods and between groups was found to be statistically significant (p<0.001).(table- 4a , 4b)

Table 5. 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

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 withdrawal or change of treatment.(table-5)

DISCUSSION:

In the present study, 75 patients of OA knee diagnosed according to ACR guidelines [15] were enrolled. These patients were randomized into two groups, Group 1 patients were put on Rose hip extract 750 mg two capsules twice daily orally in addition to standard treatment for 6 weeks while Group 2 the patients were put on placebo twice daily and standard treatment orally for 6 weeks. Current study results revealed that the maximum number of patients were in the age group of 40-59 years. Similar results were reported where average age of patients was between 52.80± 4.55 to 53.61± 5.64.[16] 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 the studies done by 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.[17]

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%. Higher prevalence of OA in females is because of hormonal factors affecting women during menopausal phase.[18] Women with co-morbid osteoporosis are also at higher risk of developing OA.[19] Demographic profile showed higher prevalence of OA in urban population than rural population. Similar results were seen in studies done where significant differences were seen in its prevalence in rural (32.6%) and urban areas (60.3%).[20] 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. Bilateral involvement of Joints in both groups was more common in current study.

Pain parameters showed improvement in both groups on WOMAC scale. The post drug values decreased in both groups at all levels i.e 0, 4, 8 and 12 weeks respectively (p value<0.001). However on inter group comparison Group A was more efficacious than Group B in reducing pain (p value < 0.001).These results were similar to that found in a randomised controlled trial involving 100 patients with painful, radiographically verified osteoarthritis of the hip or knee randomised to receive either 2.5 g standardised rosehip powder or placebo twice daily for 4 months which showed that in comparison with placebo, rosehip powder significantly reduced pain (p=0.035) and improved hip flexion as well as external rotation although last two parameters were outside the purview of our study.[21] Stiffness also showed improvement in both groups on WOMAC scale. The post drug values decreased in both groups at all levels (p value<0.001). However on inter group comparison Group A was more efficacious than Group B in reducing stiffness (p value < 0.001. A double blind, placebo controlled, crossover study done involving 112 patients with osteoarthritis of the hip, knee, hand, shoulder or neck

also showed that compared to those receiving placebo, patients who received 5 g/day of standardised rosehip powder for 3 months experienced significant reductions in stiffness ($p < 0.001$) as well as improvement in general well being including mood, sleep quality and energy.[22] However these parameters are outside the purview of our study.[22] Mean total WOMAC score also showed improvement in both groups. The post drug values decreased in both groups at all levels (p value<0.001). However on inter group comparison Group A was more efficacious than Group B in reducing total score ($p < 0.001$). Results of our current study are contrary to the study wherein while comparing rose hip powder with placebo among patients of OA, no significant differences were seen along parameters like pain and stiffness.[23] 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.

A particular galactolipid – GOPO® – has been shown to be the active principle responsible for the observed in vitro inhibition of chemotaxis and chemiluminescence of human peripheral blood leucocytes without any toxicity to the cells.[24] A specific galactolipid, monogalactosyl diacylglycerol 1, present in rose hip is believed to be responsible for its analgesic properties.[25] Besides anti-inflammatory, rose hip has also been shown to possess anti-oxidant activity that includes protective effects against oxidative stress, enhanced activity of antioxidant enzymes such as superoxide dismutase and catalase, and protective effects on gap junction intercellular communication.[26] Regarding safety, both the regimes were generally well tolerated. 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. These results were similar to that found wherein they found no major side effect in both rosehip and placebo groups.[27] 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.[28] The result of our present study has also showed that rose hip extract when added to Paracetamol has excellent efficacy as compared to placebo in Osteoarthritis. In terms of safety also, it has no additional safety concerns. 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 patients of OA knee as it produces better efficacy compared to placebo as evaluated by WOMAC score of joint pain, stiffness and physical function.

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