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Oxaceprol Monotherapy versus Oxaceprol and Glucosamine Combination Therapy for Knee Osteoarthritis

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Abstract

Introduction: Osteoarthritis (OA) is the commonest form of arthritis which presents with joint pain and functional limitations. Oxaceprol, a derivative of hydroxyproline, inhibits leukocyte migration into the joints thus inhibiting inflammatory process. Oxaceprol also increases availability of Glucosamine and improving uptake of Glucosamine and Proline in chondrocytes. **Aims and Objective:** To demonstrate efficacy of Oxaceprol Monotherapy versus Oxaceprol and Glucosamine combination therapy in patients diagnosed with Knee Osteoarthritis (KOA). **Materials and Methods:** This was an open labelled, parallel group, Randomized Controlled Trial where 40 adults age ≥50 years diagnosed with KOA randomly received either Oxaceprol 600mg OD for 4 weeks, or combination of Oxaceprol 600mg OD and Glucosamine Sulphate 1500mg OD for 4 weeks. The patients were analysed as per the differences between WOMAC scale scores, and visual analogue scale (VAS) recording from baseline to 4 weeks of treatment. **Results:** Our study showed that both Oxaceprol monotherapy (group A, n=20), and Glucosamine plus Oxaceprol combination therapy (group B, n=20) improved joint pain, stiffness, and functionality as shown by analysing WOMAC scores before, and after 4 weeks of treatment. Interestingly, VAS scores, though improved in both the groups individually, were not significantly different from each other. Conclusion: Regardless of limitations, we conclude that the efficacy of Oxaceprol and Glucosamine combination therapy is better than Oxaceprol monotherapy. Further studies are required to examine mechanism of this effect at cellular level.

Keywords: Glucosamine, Knee, Nutraceuticals, Osteoarthritis, Oxaceprol, Pain, Supplement, WOMAC, VAS, Visual Analogue Scale

1. Introduction

Osteoarthritis (OA) is described by World Health Organisation (WHO) as a chronic disease where root cause of signs and symptoms is deterioration of cartilage of joints which results in rubbing of bones with each other leading to pain, stiffness, and impaired joint movements[1]. OA is one of the major cause of disability which negatively impacts patient's Quality of Life (QOL)[2]. The joint pain is characterized as mechanical, or related to activity, but can also occur while resting in advanced cases. The pain is often deep seated, and not localized well. There is short lived stiffness which follows inactivity of the joint, as well as reduced joint movements. The joint is often instable, deformed, swelled, and accompanied by crepitation[3,4].

Older age is a well-known risk factor for OA. An estimate of 10% to 15% of population above 60 yrs. of age has some level of OA, with women affected more than

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men. In the US, an estimate of 14 million people have symptomatic Knee OA (KOA), where more than half those are under 65 years of age[3, 2]. In India, 28.7% of population was found to have KOA[5]. Apart from aging, joint trauma, obesity, decreased physical activity, biochemical factors and heredity are other etiological causes for developing OA[3,6]. Pathological development of OA indicates involvement of Metalloproteases, like collagenase, stromelysin, which degrade extracellular matrix. The breakdown products of cartilage matrix are released into synovial fluid, which promote synovial inflammation. The inflammation process result in release of proinflammatory cytokines like interleukin-1β, and TNF-α which form the vicious cycle of further joint destruction[7]. Keeping in goal of reducing pain, stiffness, and joint function, as well as alleviating pathological process at cellular level, the treatment of OA include combination of physical therapy, analgesics and anti-inflammatory drugs, and surgical intervention wherever necessary. Nonsteroidal anti-inflammatory drugs (NSAIDs), because of their ability to inhibit prostaglandins production, are the most commonly used analgesics and anti-inflammatory agents[8]. A short-term use of weak opioids, such as tramadol, for severely symptomatic OA patients is also recommended. There is good evidence that tramadol works if prescribed properly. Corticosteroids, like Methylprednisolone Acetate (MA), Triamcinolone Acetate (TA), Triamcinolone Hexacetonide (TH), Betamethasone Acetate (BA), Beta-Methasone Sodium Phosphate (BSP), and Dexamethasone (CS), interrupt the inflammatory process at multiple levels by decreasing production and action of IL-1, leukotrienes, prostaglandins, and metalloproteinases[9]. The analgesic efficacy of duloxetine, a Selective Serotonin Norepinephrine Reuptake Inhibitor (SNRI) has also been demonstrated which is due to its effect on endogenous pain-inhibitory pathway[10]. Apart from pharmaceutical agents, beneficial effects of nutraceuticals, like Glucosamine Sulfate, Chondroitin Sulfate and avocado/ soybean unsaponifiables are well known in supporting treatment of OA[11].

Different preparations of Glucosamine have been used as supplement for OA, alone or in combination of other agents like Chondroitin Sulphate. Glucosamine Sulphate has shown to arrest NF-κB activity, and the ranslocation of p50 and p65 in human chondrocytes[12]. The effectiveness of Glucosamine in improving clinical status in OA patients is still debatable. While publications in favour of Glucosamine supplement in OA have been produced showing reduction in joint pain or improvement in joint functionality[13-15], many studies also rejected beneficial outcomes of Glucosamine or its combination with other supplements[16-18]. Pharmacokinetic studies of glucosamine have raised issue that the currently recommended dosage of Glucosamine (for example, 1500 mg/d) doesn't reach the plasma, as well as the joint in desirable therapeutic concentration, which can explain lower efficacy of the drug[19].

Oxaceprol is derived from L-proline and has been in use over several years in patients with OA. It has shown efficacy equivalent to NSAIDs, but devoid of Adverse Effects (ADRs) related to Prostaglandins (PG) synthesis shown by NSAID[20,21]. It is known to reduce inflammatory process by reducing leucocyte recruitment, and adhesion to endothelium. This maintain endothelial integrity, and prevent microvascular leakage due to inflammation[22-24]. Apart from these effects, Oxaceprol has also shown to increase Glucosamine and Proline update into chondrocytes, as well as, increase their absorption into the macromolecular structures in matrix of the cartilage[25]. Keeping in mind the anti-inflammatory effects of Oxaceprol, and enhancement of Glucosamine uptake in the chondrocytes, we planned a study to analyse clinical effectiveness of Glucosamine in combination with Oxaceprol.

2. Methods

This was an open labelled, parallel group, Randomized Controlled Trial where adults age ≥50 years diagnosed with KOA who visited Orthopaedics OPD at Rajindra Hospital, Patiala were enrolled in the study after signing of informed consent. The trial was approved by Institutional Ethics committee.

The diagnosis of KOA was made clinically, and with the help of radiograph which confirmed joint degenerative changes. The patients should also be having minimum reading of 35 mm on a 100 mm Visual Analog Scale (VAS) for last 3 months. The exclusion criteria was presence of osteoarthritis due to any other causes than ageing, like trauma; intervention with intra-articular steroids, or hyaluronic acid with last 3 months; osteoarthritis grade 4 in Kellgren Lawrence grading system[26]; arthroscopy within last 6 months; any serious co-morbidities.

The eligible patients were randomized with the help of coin-flip method into two groups in 1:1 ratio, 20 patients

each in group I and group II. At the baseline, the condition of the patients was recorded with the help of WOMAC scale and VAS. A 7-day washout period of drug was done if patients were already having pharmacotherapy with analgesics. The patients in group I received Oxaceprol 600 mg OD for 4 weeks. The group II received combination of Oxaceprol 600 mg OD, and Glucosamine Sulphate 1500 mg OD for 4 weeks. At the end of the study period, the patients were interviewed again according to the questionnaire of WOMAC scale, and with VAS. Any changes in the functionality of the affected joint was done by comparing reading from WOMAC scale, and VAS from baseline to 4 weeks of the therapy.

The statistical analysis of normally distributed data of WOMAC score was done by student's T test. The interpretation of VAS was done according to the following categorizations: 0 to 4 mm was considered as "no pain"; 5 to 44 mm, as "mild pain"; 45 to 74 mm, as "moderate pain"; and 75 to 100 mm, as "severe pain"[27]. The VAS was analysed by student's t test based on measurement on the mm scale. Both the tests were 2-tailed, and p value <0.05 was considered to be statistically significant.

3. Results

A total of 40 patients were enrolled in the study who were eligible based on inclusion criteria. Age of the patients were 55.4±51 in group A, and 56.1±32 in group B. Overall, percentage of female patients (66%) was more than male patients (34%). The WOMAC scores recorded at the baseline were similar in both the groups. Table 1, figures 1 to 3, show WOMAC scores comparison between baseline and 4 weeks of treatment within the two groups, as well as comparison between the two groups. The statistical analysis of the scores show significant reduction in the WOMAC scores of joint pain, stiffness, and function, from baseline to 4th week of the treatment in both the groups. The Group B showed significantly lower WOMAC scores at the end of the study as compared to Group A.

Table 2 shows analysis of VAS scores. The group A, as well as group B showed comparable measurements of VAS. There was significant reduction in VAS readings after 4 weeks of treatment in both the groups, however, we observed no significant difference in the measurements between the two groups after the treatment (p=0.10).

4. Discussion

Osteoarthritis is one of the most common form of disability largely affecting older age group. There is chronic deterioration of joint function, along with pain and stiffness. NSAIDs are widely used for control of pain, as well as inflammatory process occurring in the affected joints. The success of NSAIDs in controlling signs and symptoms of the disease is not devoid of adverse effects related to inhibition of prostaglandins as mechanism of action. Other drugs like opioids, glucocorticoids, duloxetine, and some nutritional supplements are in use but with limited efficacy.

Glucosamine is a neutraceutical, use of which, although debatable[28], is attributed to its ability to inhibit NF-κB activity, and the translocation of p50 and p65 in human chondrocytes[12]. The issue of concentration of glucosamine reaching insufficiently in joint spaces has been shown in its pharmacokinetic studies, which results in its inadequate efficacy[19].

Table 1. WOMAC scores of Group A and Group B.

	GROUP	BASELINE	4 WEEKS	P value baseline vs 4 weeks
WOMAC pain	A	16.60±1.35	10.60±8.9	<0.0001 (S)
	B	15.9±1.33	8.9±1.23	<0.0001(S)
	Between Group P value	0.107 (NS)	0.014 (S)	
WOMAC stiffness	A	4±1.17	2.95±1.31	0.018 (S)
	B	3.65±0.99	2.15±0.99	0.0007(S)
	Between Group P value	0.31 (NS)	0.005 (S)	
WOMAC function	A	50.75±7.16	24.9±7.16	<0.0001(S)
	B	50.50±7.0	20.25±3.78	<0.0001(S)
	Between Group P value	0.91 (NS)	0.016(S)	

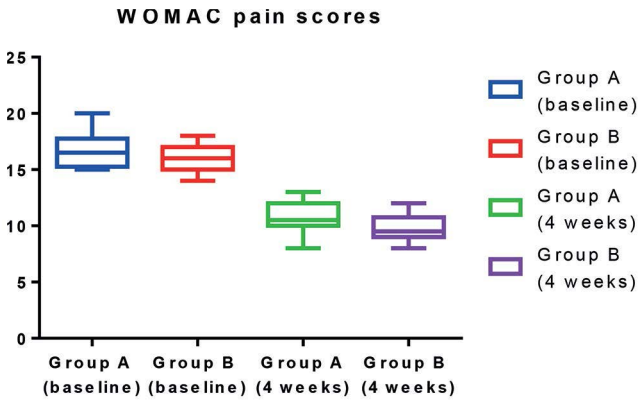

Figure 1. WOMAC Pain Scores.

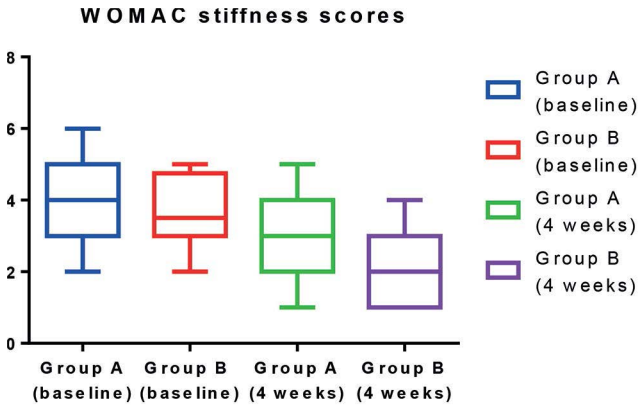

Figure 2. WOMAC Stiffness Scores.

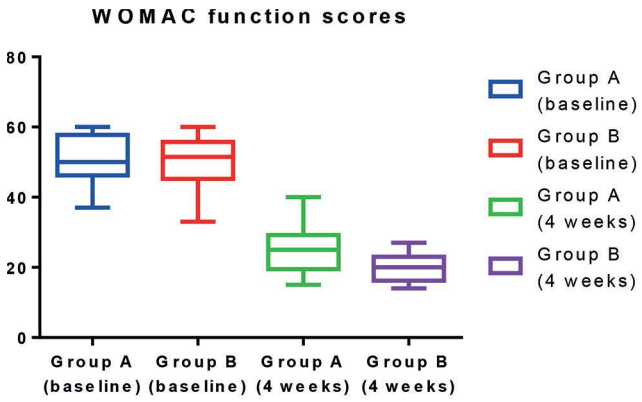

Figure 3. WOMAC Function Scores.

Oxaceprol, a proline derivative has been in use for OA from almost three decades, is not a popular treatment option in India. Its effectiveness is similar to Diclofenac, a NSAID[29,20], and Tramadol, an opioid[30], as well as, it is devoid of ADRs related to these drugs. It reduces inflammatory process by inhibiting leukocyte rolling, leukocyte adherence, granulocytes infilteration, activation of complement system, edema formation, vasculitis, and synovial membrane proliferation[21-24]. Apart from that, it also improves cellular and bone matrix, stimulate metabolism of cartilage proteoglycan, and enhanced incorporation of glucosamine and proline in chondrocytes, and cartilage matrix[21,25].

We planned this study to examine effect of combination therapy of Oxaceprol and Glucosamine, as compared to Oxaceprol monotherapy in patients with OA. As shown by Kalbhen D, et al., Oxaceprol increases uptake of Glucosamine in chondrocytes[25], therefore, we planned this study to examine whether combination therapy of Oxaceprol and Glucosamine showed better clinical improvement in knee OA patients when compared with Oxaceprol monotherapy or not.

Our results showed that both Oxaceprol monotherapy (group A, n=20), and Glucosamine plus Oxaceprol combination therapy (group B, n=20) improved joint pain, stiffness, and functionality as shown by analysing WOMAC scores before, and after 4 weeks of treatment. The combination therapy also showed significantly better efficacy than Oxaceprol monotherapy by the end of the study. Interestingly, VAS scores, though improved in both the groups individually, were not significantly different from each other.

Oxaceprol have been studied as monotherapy, as well as different combinations, but not in combination with Glucosamine in particular. Our study is first one to analyse this combination and finds combination therapy of Oxaceprol and glucosamine significantly better than Oxaceprol monotherapy. We used WOMAC scores in our study which is a reliable and validated scale to measure effects of treatment in OA patients[31,32]. The expression of

Table 2. Visual Analogue Scale results of Group A and Group B

VAS score	Before treatment Group A (i)	After treatment Group A (ii)	Before treatment group B (iii)	After treatment group B (iv)	P value (i) vs (ii)	P value (iii) vs (iv)	P value (i) vs (iii)	P (ii) vs (iv)
Mean ± SD	55.00±24.6	45.50±21.48	56.00±23.08	35.50±15.70	<0.0001	<0.0001	0.89	0.10

pain is multifaceted which is not only related to pathology of the disease, as well as its affect component. Therefore, we also used VAS scale to examine patients' satisfaction with outcome of the treatment, which is a reliable method for the same . Both the instruments of analysis we used have been regularly in use in various clinical studies. The significant reduction of WOMAC scores in Group B show results in favour of Glucosamine and Oxaceprolcombination therapy against Oxaceprol monotherapy. The VAS scale did not show remarkable differences in patients' satisfaction of treatment outcome when both the groups were compared, which is not in line with results of WOMAC scale. Patient's satisfaction of outcome doesn't only depend on clinical improvement, but also on various other factors like mental health, sociodemographic, and patient information consultation[34]. Analysis of all these factors was beyond the scope of the present study.

Our study also has its share of limitations. The study was conducted only at single center with limited number of sample size. Osteoarthritis, which is a chronic disease, should be evaluated for longer period of time to establish effects of any treatment. The instruments we used in our study were meant only to evaluate clinical outcome, and patient's satisfaction of outcome, but not to consider mechanism of action of the therapy. It is still questionable, whether the combination therapy showed better results due to increased uptake of glucosamine by Oxaceprol, or any other factor. Therefore, further studies with bigger sample size, multiple center of recruitment of patients, and use of histological analysis are recommended to establish findings of our study.

5. Conclusion

Regardless of limitations, we conclude that the efficacy of Oxaceprol and Glucosamine combination therapy is better than Oxaceprol monotherapy. Further studies are required to examine mechanism of this effect at cellular level.

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