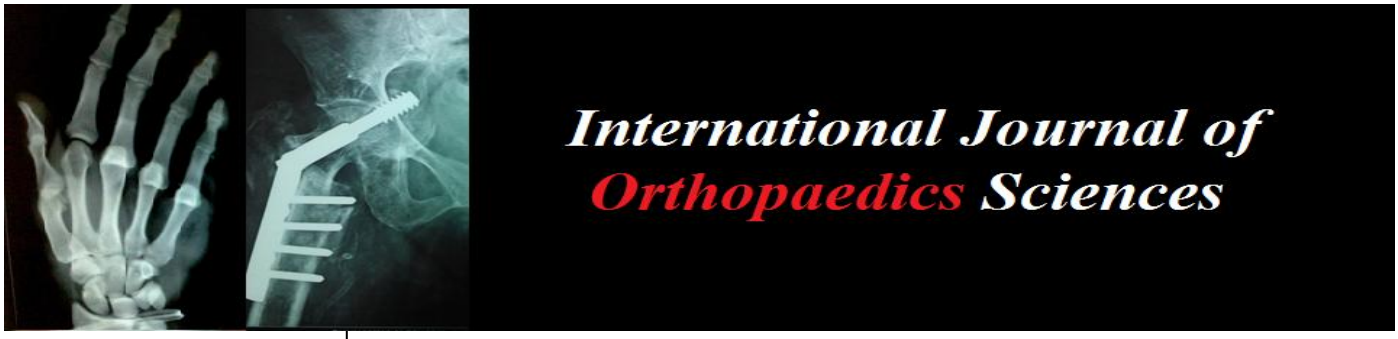

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Evaluation of clinical efficacy of undenatured type ii collagen in the treatment of osteoarthritis of knee. A randomized controlled study

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Abstract
Background: One of the leading diseases among the elderly population is Osteoarthritis of Knee, which occurs due to the destruction of articular cartilage by immunologic or mechanical factors. Collagen is the most abundant component of the cartilage. Collagen derivatives have shown to have disease modifying action in osteoarthritis. This study evaluates the ability of Undenatured Type II Collagen to improve knee symptoms in patients diagnosed with Osteoarthritis of knee.
Method: A total of 60 patients who satisfied our inclusion and exclusion criteria were randomly distributed in two groups. One treated with 1500 mg/day of acetaminophen (group A; n=30) and the other treated with 10 mg/day of native type II collagen (group UC-II; n=30) for 3 months. Visual Analogue Scale (VAS) at rest and during walking, Western Ontario McMaster (WOMAC) pain and WOMAC function were recorded.
Results: After 180 days of treatment, although there was overall reduction in WOMAC groups AC+ UC-II was significantly better than AC for "night pain" (p= 0.040) and "resting pain" (p= 0.025). AC+ UC-II was significantly better than AC for "ascending stairs at 60 days and 180 days" (p=0.020 & 0.035 respectively), "at night while in bed" (p=0.020) at 60 days and difficulty walking on flat surface at 180 days (p=0.036). AC and UC-II was most effective and reduced VAS & WOMAC scores by 30%.
Conclusion: The results suggest that undenatured type II collagen treatment combined with acetaminophen has more marked effect when compared to only acetaminophen for symptomatic treatment of patients with knee osteoarthritis.

Keywords: Undenatured Type II collagen, visual analogue scale, WOMAC, osteoarthritis of knee

Introduction
Osteoarthritis is one of the most prevalent chronic musculoskeletal conditions worldwide. It is a common cause of pain and disability among many patients. Other symptoms of osteoarthritis include stiffness and reduced movements. Overall the disease results in impaired quality of life. Coupled with high prevalence and associated morbidity, the disease seeks attention at personal as well as national and even global level [1]. Osteoarthritis pathophysiology involves the whole joint in a disease process that includes focal and progressive loss of hyaline articular cartilage. Concomitant changes in the bone underneath the cartilage involve formation of osteophytes and bony sclerosis, as well as alterations in the synovium and joint capsule. Cartilage loss or degeneration may be a result of natural aging, obesity, repeated trauma or hormone disorders. The mechanical stress on the damaged joint irritates and inflames the cartilage causing joint pain and swelling [2]. UC-II is a natural ingredient which contains a glycosylated, undenatured type-II collagen. Previous studies have shown that small doses of UC-II modulate joint health in both OA and RA [3]. Oral administration of cartilage derived type I1 collagen (CII) has been shown to ameliorate arthritis in animal models of joint inflammation, and preliminary studies have suggested that this novel therapy is clinically beneficial and safe in patients with rheumatoid arthritis (RA) and Osteoarthritis (OA) [4].

Materials and method
Study Design: This study was designed as a prospective randomized Interventional study with a three month follow- up period which was conducted on out patients with Osteoarthritis of

knee in Department of Orthopedics at KIMS Hospital and Research Centre from Aug 2019 to Feb 2020.

Inclusion criteria

- Patients between the age 45-70 years with the diagnosis of primary knee OA according to the American College of Rheumatology (ACR) criteria and Kellgren Lawrence radiological stage II or III will be included in the study.

Exclusion criteria

- Intra-articular injections or physical therapy within the last year to a previous lower extremity.
- Surgery, oral treatment with glucosamine and/or chondroitin or other natural health products within the last month, synovitis and effusion in the knee, serious concomitant systemic diseases, peripheral or central neurological disorder, hypersensitivity to acetaminophen or severe cardiac, renal, hepatic or hematologic disease.

Sample size calculation

- From reference to literature, we assumed a standard deviation change of 1.16 and minimum clinically important difference of 82% on WOMAC Scale.
- At 5% level of significance and 80% power of test, ß of 0.2, the sample size was calculated which resulted in the need of 30 patients. Hence the total sample size was calculated to be 30 patients per group

Study groups and data collection

A total of 60 patients were enrolled in the study as per the eligibility criteria. All the patients were informed about the purpose of the study and the requirement of the study and details of the drugs. Written informed consent was obtained from the patients. The study was conducted in accordance with declaration of Helsinki and was approved by KIMS Ethics committee.

A complete physical examination was performed. Activity level, diet history, medication/supplement use and medical history were recorded in a specially designed form. The VAS score, the WOMAC Index were assessed. One of the most frequently used pain rating scales is the visual analog scale (VAS). The VAS is a one- dimensional scale, with several appealing characteristics. It is easy to use, requires no verbal or reading skills, and is sufficiently versatile to be employed in a variety of settings [5]. Subjects were instructed to get an X-ray of the affected knees to confirm the diagnosis. The patients were randomly distributed into two groups:

Group A: Standard care - treated with Analgesic

Group B: Test group -treated with analgesic with 10 mg/day of native type II collagen.

All the patients were instructed not to apply force on their knees while working or during other activities. During the study period, their compliance to the treatment was assessed weekly through phone calls.

Clinical endpoints

The primary endpoint was defined as the change in total WOMAC score from baseline through day 180. Secondary clinical endpoints encompass (1) mean VAS; (2) mean WOMAC subscales scores.

Baseline and follow up scores of VAS, WOMAC will be recorded to assess the effectiveness of the intervention.

Statistical analysis

Statistical analysis was performed using programs available in the Microsoft Excel version 2013. The descriptive data were represented with n (sample size), mean and standard deviation for continuous variables. Chi-square analyses were used for categorical variables. To compare AC with UC-II linear contrast was included in the Analysis of Variance.

Furthermore, comparisons between the UC-II and AC groups were made at each visit using Analysis of Variance, using the baseline visit as a covariate. P value less than 0.05 (p<0.05) was considered significant.

Results

Table 1: Demographics characteristics of patients of two groups.

Variable	Group AC (n=29)	Group AC (N=30)
Age (Years)	64.5±6.58	66.9±8.99
Gender Male	9	10
Female	21	20
KGL scale Stage 2	27	27
Stage 3	2	3
Disease Duration(Years)	4.20±1.42	3.55±1.75

Demographics of the patients are summarized in Table 1. The overall demographic characteristics were almost similar in terms of age, Gender, KGL scale and Disease duration. There was no significant difference among the demographic characteristics with KGL scale and disease duration.

VAS score

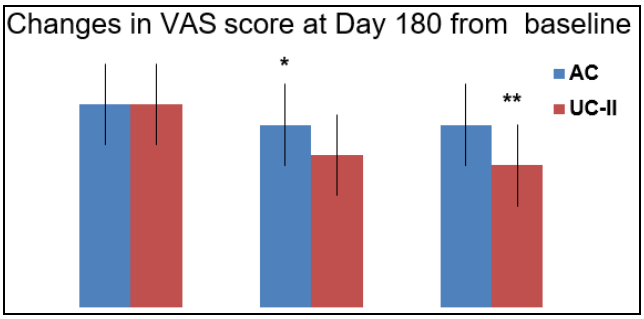

Fig 1: Changes in VAS score at Day 180 from baseline. VAS scores from each treatment group were compared to baseline value at 0, 60, 180 days. Each bar represents mean± SEM. ** p < 0.05 indicates significant difference from the baseline.

The differences in the scores between baseline and treatment visits were not significant for all VAS scores. However, the treatment group with AC+ UC-II treatment had a significant effect for "pain while climbing up and down stairs" and "night pain" (p= 0.024 and 0.035 respectively). When groups were compared at each visit, AC+ UC-II was significantly better than AC for "night pain" (p= 0.040) and "resting pain" (p= 0.025). Although both the treatments reduced the VAS scores, AC+ UC-II was found to be more effective with a 30% decrease after 180 days of treatment compared to 20% decrease in AC treated groups.

Within groups analysis showed that subjects on AC+ UC-II showed a significant reduction in total VAS scores at day 60 and day 180 as compared to baseline. However, subjects on AC showed a significant reduction in total VAS scores at Day 60 and no significant difference was observed at Day 190 when compared to baseline.

WOMAC score

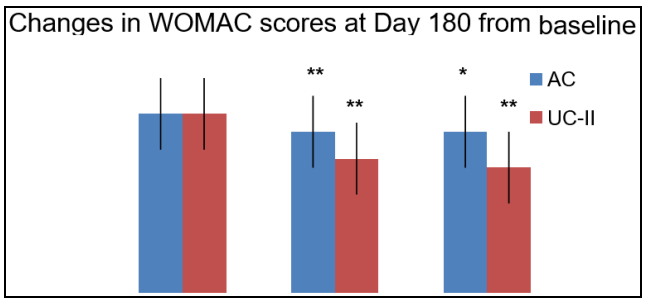

Fig 2: Changes in WOMAC score at Day 180 from baseline. WOMAC scores from each treatment group were compared to baseline value at 0, 60, 180 days. Each bar represents mean± SEM. $p < 0.05$ indicates significant difference from the baseline.

The interaction between visit and treatment was significant in AC+ UC-II treated group for "pain while walking on flat surface" (p=0.030), "difficulty while walking on flat surface" (p=0.028) and "performing heavy domestic duties" (p=0.035) as compared to AC treated group.

Results also showed that AC+ UC-II treatment has a significant effect for “ascending stairs” (p=0.012) as compared to AC treatment. Additionally, when groups were compared at each follow-up, AC+ UC-II was significantly better than AC for “ascending stairs at 60 days and 180 days” (p=0.020 & 0.035 respectively), “at night while in bed” (p=0.020) at 60 days and difficulty walking on flat surface at 180 days (p=0.036). There were no further statistically significant differences for any other individual WOMAC components or summary scores.

Treatment with AC+ UC-II was most effective and reduced the WOMAC scores by 30%.

Discussion- Osteoarthritis is the most widespread joint-affecting disease. Patients with osteoarthritis experience pain and impaired mobility resulting in marked reduction of quality of life [6]. A clinical trial showed that chicken type II collagen (CCII)exhibitsintriguing possibilitiesforthe treatment of autoimmune diseases by inducing oral tolerance [7].

Two studies conducted by Reginster JY *et al*, and Pavelká K at.al, showed that gluosamine sulphate was effective as a disease modifying agent in osteoarthritis. Further studies compared the efficacy of Glucosamine sulphate and Undenatured-Type II Collagen in reducing the symptoms and improving the qua;ity of life in patients with Osteoarthritis of knee [8, 9]. Our study successfully evaluated the efficacy of Undenatured Type –II Collagen in reducing the pain and assessing the severity of pain in rest as well in functional abilities. The results showed the clear improvement in the outcome in the patients treated with AC+ UC-II.

A review by Crowley *et al*, indicated that UC-II treatment was more efficacious resulting in a significant reduction in all assessments from the baseline at 90 days; whereas, this effect was not observed in G+C treatment group. Specifically, although both treatments reduced the Western Ontario McMaster Osteoarthritis Index (WOMAC) score, treatment with UC-II reduced the WOMAC score by 33% as compared to 14% in G+C treated group after 90 days. Similar results were obtained for visual analog scale (VAS) scores. Although both the treatments reduced the VAS score, UC-II treatment decreased VAS score by 40% after 90 days as compared to 15.4% in G+C treated group [10].

In a study conducted by Fulya Bakilan *et al*, showed that after 3 months of treatment, significant improvement compared to baseline was reported in joint pain (VAS walking), function (WOMAC) and quality of life (SF-36) in the AC+CII group, while only improvements in some subscales of the SF-36 survey and VAS walking were detected in the AC group. Comparisons between the groups revealed a significant difference in VAS walking score in favour of the AC+CII group as compared to AC group [11].

Another study by James P. Lugo, Zainulabedin M. Saiyed, Nancy E. Lane showed that at day 180, the UC-II group demonstrated a significant reduction in overall WOMAC score compared to placebo. Supplementation with UC-II also resulted in significant changes for all three WOMAC subscales: pain, stiffness, physical function [12].

Conclusion

Osteoarthritis is the major clinical concern in Indian population. The study found that undenatured type II collagen, significantly improved knee function in OA patients by day 180, than acetaminophen alone and was tolerated better. Furthermore, studies should be made to evaluate the best alternatives that could overcome the pain during exercise etc. Undenatured type II collagen has been used widely because of its safety profile.

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