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Viscosupplementation with Hyaluronic acid as an Adjuvant to Diacerein in improving Pain, Stiffness and Physical function in Primary Osteoarthritic Knees: a 1 year follow-up observation study

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Abstract: *Background:* In the arthritic joint, the concentration and molecular weight of hyaluronic acid are decreased by 33% to 50% because the synthesis of hyaluronic acid in OA is disrupted by increased levels of pro-inflammatory cytokines, free radicals and proteinases. The American College of Rheumatology guidelines for the treatment of osteoarthritis of the knee recommended that one treatment option to be considered is the use of intra-articular injections of hyaluronic acid for the relief of osteoarthritic pain. *Objective:* To describe the patient characteristics and the add-on clinical effect of viscosupplementation on physical function, pain and stiffness in patients receiving diacerein for primary knee osteoarthritis. *Methods:* The study recruited 39 primary osteoarthritis patients suffering from the OA for at least 6 months of which 18 were male and 21female patients age range 40-80 years and classified according to the Kellgren-Lawrence system of Grade 2-3. Intra-articular hyaluronic acid supplementation in target knee was given in OPD setting over 5 weekly doses. *Results:* Intensity of knee pain, stiffness, physical function of knee joint shows significant improvement for 6 months of intra-articular hyaluronic acid supplementation and non significant improvement till 1 year of follow up in primary osteoarthritic knees. *Conclusion:* Intraarticular hyaluronic acid viscosupplementation along with diacerin is an effective combination in the management of chronic OA pain, stiffness and maintaining physical functions over long time.

Keywords: Osteoarthritis, Kellgren-Lawrence system of Grade, Intra-articular Hyaluronic Acid.

Introduction

Knee OA is one of the most common joint disorders and causes considerable pain and immobility [1]. In primary O.A. there are no underlying predisposing factors where as in secondary there is a predisposing factor that causes the disease. The normal adult knee contains approximately 2 ml of synovial fluid, with a HA concentration of 2.5 to 4.0 mg/ml whose function is both mechanical and metabolic.

HA provides important viscoelasticity and lubricating properties to synovial fluid, thereby reducing articular cartilage wear and acting as a lubricant during slow movements and as a shock absorber during rapid movements [2-5]. In the arthritic joint, the concentration and molecular weight of HA are decreased by 33% to 50% because the synthesis of HA in OA is disrupted by increased levels of pro-inflammatory cytokines, free radicals and proteinases [2, 6]. Potential disease-modifying activities of the HA include promotion of healing and repair by stimulating chondrocyte growth and stimulating synthesis of cartilage matrix components: collagen, proteoglycans and endogenous hyaluronans[2-5]. The synergistic effect of exogenous HA reduces the mechanical, chemical or thermal noxious stimuli to the innervated tissues of the synovial joint restoring normal homeostasis and reducing pain and stiffness [3].

Previous guidelines for the treatment of knee osteoarthritis recommended the use of HA only in patients who have not responded to non-pharmacologic therapies and simple analgesics, and after the unsuccessful trial of NSAIDs and selective COX-2 inhibitors [7-8]. HA therapy is recommended in the *American College of Rheumatology (ACR)* and *European League of Arthritis & Rheumatism (EULAR)* guidelines for the management of

patients with hip or knee OA, and is advocated for use in those patients who have not responded to other therapies [8-11].

The American College of Rheumatology diagnostic criteria are;

Clinico-radiological knee osteoarthritis if 1, 2 or 1, 3, 5, 6 or 1, 4, 5, 6 are present:

1) Knee pain for most days of previous month.
2) Osteophytes at joint margins on x-rays.
3) Synovial fluid typical of osteoarthritis.
4) Age 40 years or older.
5) Crepitus on active joint motion.
6) Morning stiffness lasting 30 min or less.

Clinical knee osteoarthritis if 1, 2, 3, 4 or 1, 2, 5 or 1, 4, 5 are present:

1) Knee pain for most days of previous month.
2) Crepitus on active joint motion.
3) Morning stiffness lasting 30 min or less.
4) Age 38 years or older.
5) Bony enlargement of the knee on examination.

Guidelines on the management of knee and hip OA have been published by the American College of Rheumatology [8] and the Royal College of Physicians [11]. In 2003, EULAR commissioned a steering group to review the evidence for the treatment of knee OA [12]. The treatment of knee OA should be tailored according to: *knee risk factors (obesity, adverse mechanical factors, physical activity); general risk factors (age, co-morbidity, poly-pharmacy); level of pain intensity and disability; sign of inflammation—for example, effusion; location and degree of structural damage* [13].

OA knee *occurrence risk factors* being age, sex, physical activity, body-mass index (including obesity), intense sport activities, quadriceps strength, bone density, previous injury, hormone replacement therapy (protective), vitamin D, smoking (protective or deleterious), malalignment (including varus and valgus), genetics. OA Knee *Progression risk factors* being age, body-mass index (including obesity), vitamin D, hormone replacement therapy (protective), malalignment (including varus and valgus), chronic joint effusion, synovitis, intense sport activities, subchondral bone oedema on MRI.

Ghosh [14] demonstrated de novo HA biosynthesis by fibroblasts upon in vitro exposure to exogenous HA (similar to the synovial fluid HA is 5 to 7 × 106 Da, a high-molecular-weight glycosaminoglycan made up of repeating disaccharide units of N-acetyl-glucosamine and glucoronic acid). It also provided a protective effect on chondrocytes exposed to leukocyte proteinases, IL-1, or oxygen-derived free radicals.

Diacerein is a pro drug which gives the active metabolite rhein, which can effectively inhibit the IL-1 activated MAPK pathway and the binding of NF–Kappa and AP-1 transcription factors, two key factors involved in the expression of several pro-inflammatory genes by chondrocyte [15-16]. In addition the drug can reduce the pro-catabolic effect of the cytokine, by reducing the MMP-1 synthesis and enhance the synthesis of matrix components such as type II collagen and aggrecan [15-16]. It increases the production of transforming growth factor- b (TGF-b1 and TGF-b2) that stimulates chondrocyte proliferation and stimulates the production of collagen II, proteoglycan synthesis and increase matrix components.

The pharmacokinetics of diacerein is the same in young and elderly people with normal renal function after a single dose (50 mg) or repeated doses (25 to 75mg) twice daily. Taking diacerein with a standard meal delays systematic absorption but is associated with a 25% increase in the amount absorbed. Hence it is advisable to administer the drug with a major meal. Though dose modification is required in mild to severe renal insufficiency (50% reduction in severe renal failure) [17], no reduction in initial dose is proposed in liver cirrhosis [18]. Mean medical and sick leave costs per patient over 9 months were 829.10 in the Synvisc group and 829.40 in the conventional treatment group [19].

Aims & Objectives: To determine the clinical effect of viscosupplementation on physical function, pain and stiffness in patients receiving diacerein.

Material and Methods

Ethics: The clinical protocol followed is a generally accepted method in osteoarthritis management and as per guidelines. Written informed consents were obtained from all patients.

Study duration: 2 years (from 4/7/12 till 4/8/14)

Study protocol: A prospective clinical routine protocol followed in the Department of Physical Medicine and Rehabilitation of Dr. Ram Manohar Lohia hospital, New Delhi has been presented. At the screening visit patients gave their written, informed consent and a physical examination was performed on the knee to be treated ("target knee"). Patients were required to meet the American College of Rheumatology criteria for OA (knee pain for most days of the prior month and osteophyte(s) at the joint margin visible on weight bearing X-ray). We diagnosed the OA when pain and tenderness in combination with osteoarthritic signs according to the Kellgren-Lawrence system [20] of Grade 2-3 on basis of radiological features of joint space narrowing(JSN) and osteophytes for the tibiofemoral compartment graded from 0-3; 0=no osteophyte/JSN; 1=possible osteophyte(s)/JSN; 2=definite osteophyte(s)/JSN; 3=severe osteophyte(s)/JSN.

The study included 92 primary osteoarthritis knee patients of which 43 were male and 49 were female patients. The age of the patients were ranged between 40-80 years, suffering from the knee OA for at least 6 months. In this study demographic characteristic such as age, sex and diagnosis were recorded (Table 1). Demographic data and medical history information were collected. A thorough physical examination and laboratory investigations including serum vitamin D, complete blood count, liver function, serum electrolytes, serum creatinine, serum uric acid, blood sugar, urine analysis, stool occult blood and weight bearing X-ray of the knee joint were carried out before drug administration and after the completion of treatment.

Main inclusion criteria were: Male and female patients age > 40 years; diagnosis of primary OA of the target knee; X-ray evidence of OA in the medial and/ or lateral tibio-femoral on either/both knee; continued OA pain in the target knee despite conservative treatments; OA with primary osteopenia/osteoporosis.

Main exclusion criteria were: Secondary OA in the knee; grade I and IV radiographic stage OA (Kellgren-Lawrence grading system); clinically apparent tense effusion of the target knee; significant valgus/ varus deformities; viscosupplementation/ surgery in any joint in the past; systemic or IA injection of corticosteroids in any joint within three months prior to screening; any other co-morbidities like history of hypersensitivity to NSAIDs, history of peptic ulcer, history of bleeding disorders, renal impairment, alcoholic liver disease, pregnant or lactating woman, uncontrolled anemia, hypertension, congestive cardiac failure and bronchial asthma.

Clinical Assessments: Clinical examination along with routine blood investigations was done at screening and after 3 month, 6 month and 12 month follow up. The outcome of the therapy was based on the improvement of the clinical manifestations of osteoarthritis and tolerability of the drug.

Clinical Measurements: The task force of the Osteoarthritis Research Society has recommended the following pain measurement scales for assessment of OA of the knee. They are listed below;

a. Global knee pain score (visual analogue scale or Likert scale)
b. Knee pain on walking (visual analogue scale or Likert scale)
c. Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index [21]: A self-administered, disease-specific measure of health status. It consists of 24 questions including 5 assessing for pain, 2 for stiffness, and 17 for physical function. WOMAC is a valid and reliable measure of clinically significant changes in health status following surgical or pharmacologic interventions. Each question is assigned a score between 0 and 4. Scores from the 24 questions are summed. A higher score (highest possible score is 96) corresponds to less pain, stiffness and better function.

A lower score (lowest possible score is 0) correlates with more pain, stiffness and lower function.

Tolerability assessment was based on adverse events as well as compliance. Adverse events were monitored and noted at every visit.

Statistical Test applied: Paired student t-test

Study Treatments: All patients had been treated initially according to the practice guidelines including patient education, knee care, physical therapy and with diacerein 50mg once daily over the study period. Intra-articular supplementation with 2ml high molecular weight hyaluronic acid in target knee was given in OPD setting over 5 weekly doses under clinical supervision and safety precaution. Patients were asked to avoid excessive walking for 1 day and apply ice to avoid swelling but to report urgently if symptoms aggravated or any other complications happened. They were asked to follow up at 3months, 6months and 1year of treatment.

Results

Demographic and clinical variables of study subjects:

Table-1: Shows the changes in the various sub-scores over the period of time in patients with KL G-2

KL Grade 2 Characteristics	Diacerein KLG2 (N=23)	Diacerein +Injection KLG2(N=23) Mean(+- SD)	Unpaired Differences Mean(SD)	Unpaired t test significance	Paired Differences Mean(SD) S.D.	Pair t test significance
AGE	51.92(5.68)	60.39(12)				
Male	12	12				
Female	11	11				
BMI<25	11	11				
BMI>25	12	12				
WOMAC pain 0wk	13.71(2.156)	13.43(2.27)	-0.17(2.64)	0.755		
WOMAC pain 3mn	9.79(2.021)	7.70(1.60)	-2.04(2.05)	.0..000	5.739(1.287)	.000
WOMAC pain 6mn	8.08(1.640)	5.87(1.714)	-2.17(2.13)	.0..000	1.826(1.922)	.000
WOMAC pain 12mn	7.04(1.574)	5.39(1.777)	-1.6(2.15)	..0.002	.478(.790)	.008
WOMAC stiffness 0wk	4.75(1.113)	4.13(1.014)	-.0.57(1.16)	..0.029		
WOMAC stiffness 3mn	4.67(1.007)	3.17(0.984)	-1.44(1.08)	.0.000	.957(.367)	.000
WOMAC stiffness 6mn	4.54(.721)	2.74(0.964)	-1.78(1.08)	.0.000	.435(.590)	.002
WOMAC stiffness 12mn	4.50(.659)	2.83(0.984)	-1.65(0.88)	.0.000	-.087(.515)	.426
WOMAC physical function 0wk	50.83(4.527)	34.35(3.63)	-16.26(5.6)	.0.000		
WOMAC physical function 3mn	51.04(2.956)	47.96(2.93)	-2.96(4.16)	.0.003	-13.6(1.588)	.000
WOMAC physical function 6mn	51.04(2.386)	48.30(2.78)	-2.61(3.69)	.0.003	-.348(.647)	.017
WOMAC physical function12mn	50.92(1.442)	48.13(2.943)	-2.74(3.28)	.0.001	.174(.576)	.162

Table-2: Shows the changes in the various sub-scores over the period of time in patients with KL G-3						
KL Grade 3 Characteristics	**Diacerein KLG3(N=23)**	**Diacerein +Injection KLG3(N=23) Mean(+- SD)**	**Unpaired Differences Mean(SD)**	**Unpaired t test significance**	**Paired difference mea(SD)**	**Paired t test Sig.**
AGE	58.33(8.44)	61.31(10.39)				
Male	9	10				
Female	14	13				
BMI<25	10	10				
BMI>25	13	13				
WOMAC pain 0wk	15.57(2)	15.88(1.3)	0.5(2)	0.348		
WOMAC pain 3mn	10.8(1.6)	9.38(1.89)	-1.37(2.18)	0.024	6.5	.000
WOMAC pain 6mn	9(1.4)	6.56(1.788)	-2.43(2.33)	0.001	2.813(2)	.000
WOMAC pain 12mn	7.9(1.26)	6.13(1.784)	-1.69(2)	0.004	.438(1)	.110
WOMAC stiffness 0wk	5.24(1)	4.81(1.109)	-0.56(1.36)	0.120		
WOMAC stiffness 3mn	5.1(1)	3.88(0.885)	-1.3(1.44)	0.002	.938(0.7)	.000
WOMAC stiffness 6mn	4.9(0.625)	3.19(0.834)	-1.8(1.27)	0.000	.688(0.48)	.000
WOMAC stiffness 12mn	4.52(0.75)	3.44(1.031)	-1(1.5)	0.012	-.250(0.58)	.104
WOMAC physical function 0wk	50.76(5.23)	36(4.8)	-15.5(5)	0.000		
WOMAC physical function 3mn	51.67(3.8)	49.75(4.55)	-2(4.2)	0.066	-13.68(2)	.000
WOMAC physical function 6mn	51.43(3.33)	50.19(4)	-1.56(4.24)	0.161	-.438(0.9)	.069
WOMAC physicalfunction12mn	51.1(1.79)	50.13(4)	-1.12(4)	0.300	.063(0.44)	.580

The age at presentation of patients with KL Grade-2 varied from 48 to 72 years with M: F=24:22and BMI<25=22 & BMI>25=24. The age at presentation of patients with KL Grade-3 varied from 51 to 72 years with M: F=19:27and BMI<25=20 & BMI>5=26.

Duration of the disease: We had found that maximum patients were having the disease for 2-3 years in both the groups.

Joint compartments involvement: There were 50% of had bilateral compartment involvement, whereas only 17% of patients had unilateral compartment involvement, remaining 33% had involvement of all the compartments of the knee.

Intensity of knee pain: In patients with KL Grade-2 diacerein and intra-articular hyaluronic acid group, the mean WOMAC pain sub-score (numeric rating scale 0-20) were 13.43, 7.70, 5.87 and 5.39 at 0, 3rd, 6th and 12th months respectively for patients. The mean paired differences between 0-3 months, 3-6 months and 6-12 months were statistically significant (p=0.00). The mean unpaired differences between groups at 3 months, 6 months and12 months were statistically significant (p=0.00).

In patients with KL Grade-3 diacerein and intra-articular hyaluronic acid group, the mean WOMAC pain sub-score (numeric rating scale 0-20) were 15.88, 9.38, 6.56 and 6.13 at 0, 3rd, 6th and 12th months respectively for patients. The mean paired differences between 0-3 months and 3-6 months were statistically significant (p=0.00) and was non-significant improvement between 6-12 months of the study (p=0.110). The mean unpaired differences between groups at 0week, 3 months, 6 months and12 months were statistically significant (p=0.00).

Figure-1: Diacerein gr2OA

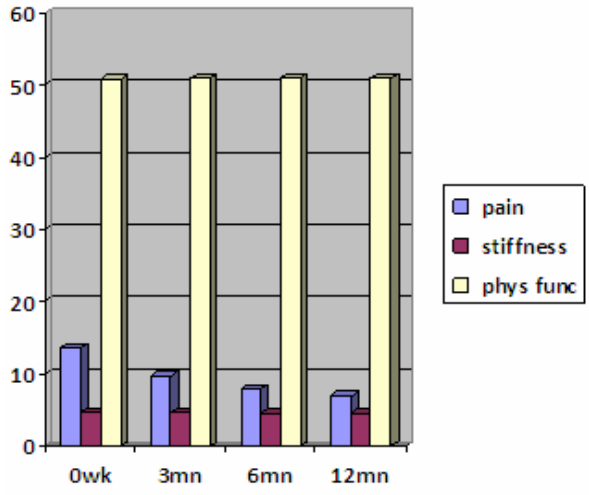


Figure-2: Diacerein+ inj.Hyaluroic acid gr2OA

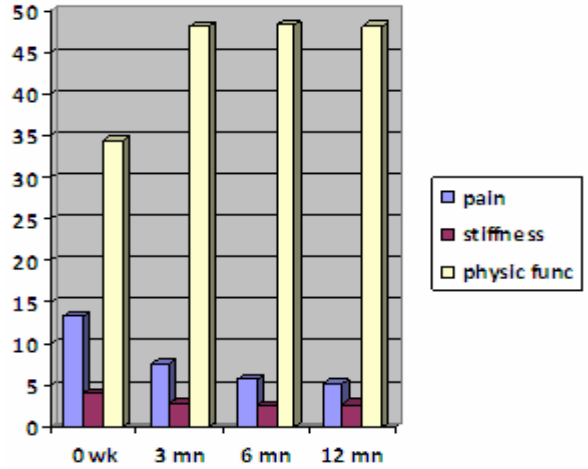


Figure-3: DIACEREIN GR3OA

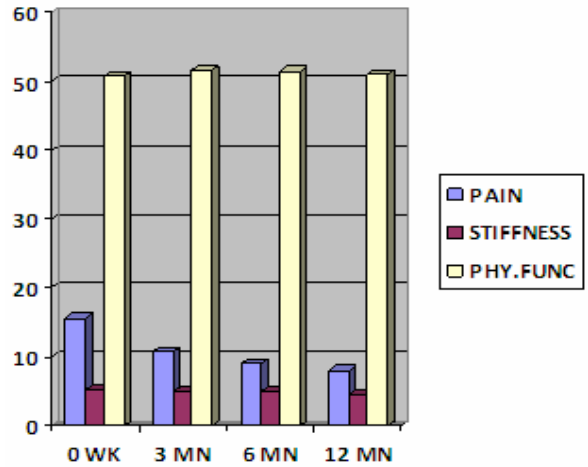
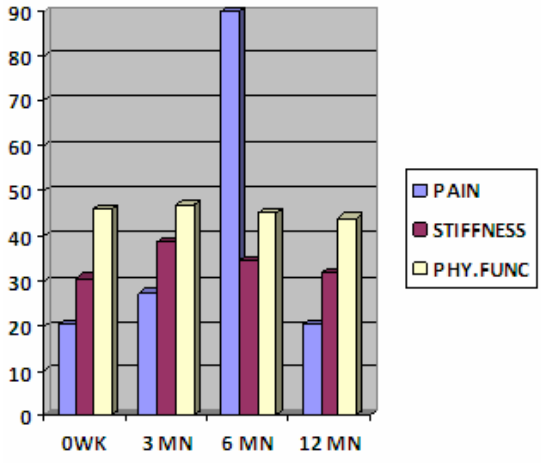


Figure-4: DIACEREIN +INJ.HYNEES GR3OA



Stiffness of knee joint: In patients with KL Grade-2 diacerein and intra-articular hyaluronic acid group, the mean WOMAC stiffness sub-score (numeric rating scale 0-8) were 4.13, 3.17, 2.74 and 2.83 at 0, 3rd, 6th and 12th months respectively for patients. The mean paired differences between 0-3 months and 3-6 months were statistically significant (p=0.00) and was non-significant improvement between 6-12 months of the study (p=0.426). The mean unpaired differences between groups at 3 months, 6 months and12 months were statistically significant (p=0.00).

In patients with KL Grade-3 diacerein and intra-articular hyaluronic acid group, the mean WOMAC stiffness sub-score (numeric rating scale 0-8) were 4.81, 3.88, 3.19 and 3.44 at 0, 3rd, 6th and 12th months respectively for patients. The mean paired differences between 0-3 months and 3-6 months were statistically significant (p=0.00) and was non-significant improvement between 6-12 months of the study (p=0.104). The mean unpaired differences between groups at 3 months, 6 months and12 months were statistically significant (p=0.00).

Physical function of knee joint: In patients with KL Grade-2 diacerein and intra-articular hyaluronic acid group, the mean WOMAC physical function sub-score (numeric rating scale 0-68) were 34.35, 47.96, 48.30 and 48.13 at 0, 3rd, 6th and 12th months respectively for patients. The mean paired differences between 0-3 months and 3-6 months were

statistically significant (p=0.00) and was non-significant improvement between 6-12 months of the study (p=0.162). The mean unpaired differences between groups at 0week, 3 months, 6 months and12 months were statistically significant (p=0.00).

In patients with KL Grade-3 diacerin and intra-articular hyaluronic acid group, the mean WOMAC physical function sub-score (numeric rating scale 0-68) were 36, 49.75, 50.19 and 50.13 at 0, 3rd, 6th and 12th months respectively for patients. The mean paired differences between 0-3 months were statistically significant (p=0.00) and was non-significant improvement between 3-6 and 6-12 months of the study (p=0.069) and (p=0.058) respectively. The mean unpaired differences between groups at 3 months and 6 months were statistically significant (p=0.00) but was non-significant improvement between 6-12 months of the study (p=0.1).

Discussion

Precautions for injection:

1) Strict aseptic technique.
2) Remove joint effusion.
3) Caution in those with allergy to avian proteins, feathers or eggs.
4) Efficacy/Safety in other joints not established.
5) Efficacy/Safety of other IA agents given concomitantly not known.
6) Efficacy/Safety in pregnant women not established.
7) Repeated exposures may have the potential for an immune response-not assessed in human.

Contraindications for injection:

1) Known allergy to avian proteins, feathers and eggs.
2) Known hypersensitivity or allergy to hyaluronans.
3) Known knee joint infection, skin disease or infection in the area of the injection site.

Pharmacological benefits & Side effect profile of the combination of IAHA with Diacerein compared to Diacerin alone: In our patients with KL Grade-2 and KL Grade-3, the mean change in WOMAC pain and stiffness sub-scores show significant efficacy of diacerein and intra-articular hyaluronic acid for knee OA pain by week 12 with a peak at week 24 reaching moderate clinical significance and residual benefit until 51 weeks compared to diacerein alone. The WOMAC physical function sub-score mean change in KL Grade-2 patients show moderate clinical significance of diacerein and intra-articular hyaluronic acid for knee OA pain at week 24 and residual benefit until 51 weeks compared to diacerin alone. The WOMAC physical function sub-score mean change in KL Grade-3 patients show moderate clinical significance of diacerein and intra-articular hyaluronic acid for knee OA pain at week 12 and residual benefit until 51 weeks compared to diacerein alone.

Table 3: Mean difference in pain and function between treatment with hyaluronic acid and treatment with placebo at 4 time points. Note: A minus indicates superiority of hyaluronic acid (a reduction of pain or functional impairment). CI = confidence interval

End point	2–6 wk	10–14 wk	22–30 wk	44–60 wk
Pain at rest, mm VAS (95% CI)	–8.7 (–17.2 to –0.2)*	–5.2 (–13.3 to 2.9)	–6.0 (–22.3 to 10.3)	–0.75 (–9.6 to 8.1)
Pain during or after exercise, mm VAS (95% CI)	–3.8 (–9.1 to 1.4)*	–4.3 (–7.6 to –0.9)	–7.1 (–11.8 to –2.4)	–0.5 (–12.5 to 11.5)
Function, z value (95% CI)	–0.00 (–0.23 to 0.23	–0.11 (–0.31 to 0.09)	–0.16 (–0.45 to 0.13)	–0.17 (–0.50 to 0.16)

Arrich [22] reported similar improvement in pain both at rest and after exercise and function at 2-6 weeks, 10-14 weeks, 22-30 weeks and maintained improvement till 44-60 weeks after hyaluronic acid supplementation. One patient in our clinic complained of increased pain after

IAHA injection 2nd dose which was managed by giving cold compression and NSAIDs for 5days and repeating the 3rd dose after a gap of 2 weeks. Also two other patients complained of soft stool, diarrhoea and mild abdominal discomfort a well known side effect with diacerein, but none of the patients dropped out as symptoms subsided within a few days even in continuing with the drug. However, there is some lower level evidence to suggest a unique safety concern for rare localized inflammatory reactions, pseudosepsis, granulomatous inflammation and severe acute inflammatory reactions (SAIR) with the cross-linked hyaluronan or hylan product [23-25].

Other mild adverse effects that have been reported include post injection itching, headaches, and calf pain [23-24]. The overall incidence of adverse events has been reported to be approximately 1% to4% per injection [23]. Brockmeir and Schaffer [26] postulated that adverse reactions are related more closely to the accuracy of intra-articular injection than to the substance itself. Avoiding surgical treatment might also prevent complications that can arise from TKR. In patients who are candidates for TKR, the need for TKR can be delayed with hylan G-F 20 when used for the treatment of OA knee pain [27].

The most common adverse event is local reaction at the injection site, consisting of mild pain, swelling, or effusion, and warmth or redness, or both. Such injection site reactions are usually mild and self-limited, resolving with 1 to 3 days and generally respond to NSAIDs and local modalities Furthermore, the incidence of adverse events with viscosupplementation is related to the injection technique used: a medial approach in a partially bent knee was associated with 5.2% adverse events by injection, compared with 1.5% with straight lateral injections [28].

Pavelka *et al*.[29] A randomised, multicenter, double-blind, placebo controlled study on 168 patients with primary end points at two months after the end of a three-month treatment period. At month 5, diacerein showed statistically significant superiority versus placebo as assessed with both the WOMAC pain (P <0.0001) and the total WOMAC (P<0.0001), demonstrating the carryover effect of the drug. This superiority was already evident from month 2 for pain (P =0.001) and month 1 for total WOMAC (P= 0.0021). Diacerein was safe and well tolerated. No serious or previously undocumented adverse events were observed during the study.

Co-morbid high BMI, osteopenia/osteoporosis and low serum vitamin D levels have been found to have a role in the progression of osteoarthritis knee. Bergink *et al* looked at a sample of 1,248 elderly people (728 women and 520 men) drawn from the Rotterdam prospective population-based cohort study [30] found a significant relation was found between 25(OH)-D3 intake and bone mineral density in association with the incidence of osteoarthritis. In case of a lower bone mineral density at the lumbar spine at baseline, an increased incidence of knee osteoarthritis was seen on radiography with decreasing vitamin D intake and serum 25(OH)-D3 levels.

Most Indian postmenopausal women showed substantial loss of DEXA femoral and spinal bone t-and z-score because of low dietary calcium intake and low serum 25(OH)-cholecalciferol levels. The Odd's ratio risk of low DEXA femoral bone t-score and z-score due to low serum 25(OH)-cholecalciferol levels is 1.04 times of normal risk [31]. Low dietary vitamin D intake increases the risk of progression of knee ROA. Particularly in subjects with low baseline BMD, vitamin D status seems to influence the incidence and progression of knee ROA. Thus, improving the vitamin D status in the elderly could protect against the development and worsening of knee OA, especially in those with low BMD.

Conclusion

Intraarticular hyaluronic acid viscosupplementation along with diacerin is a safe and effective combination in the early rehabilitation management of chronic OA pain, stiffness and maintaining physical functions and the effects last longer than diacerin alone. More recently, in 2008, the *Osteoarthritis Research Society International (OARSI)* cited intraarticular hyaluronic acid as a useful therapeutic modality, which has delayed onset, but prolonged duration of

symptomatic benefit, in treating patients with osteoarthritis of the knee or hip.

The ideal candidate for intraarticular viscosupplementation has yet to be clearly defined. However, given the cardiovascular, gastrointestinal, and renal side effects of selective and nonselective NSAIDs, the use of HA products earlier in osteoarthritis treatment paradigm should be considered.

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