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## Viscosupplementation in Osteoarthritis of Knee

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### Abstract

Osteoarthritis (OA) is a complex joint disease and is caused by inflammatory mediators, along with a process of “wear and tear of cartilage”. Osteoarthritis results in cartilage degradation, synovial inflammation, subchondral bone eburnation, degeneration of menisci, and capsular hypertrophy, which takes part in the pathogenesis of OA. Pain is the predominant symptom of OA. However the exact mechanism causing pain is multifactorial and is still not well known. Viscosupplementation with intraarticular hyaluronic acid (HA) promotes chondrocyte hyaluronic acid synthesis and prevents the further cartilage degradation and may possible help to promote the cartilage regeneration. It is also postulated to reduce the production of inflammatory mediators and matrix metalloproteinase involved in OA. Viscosupplementation reduces osteoarthritis symptoms in early to moderate OA, and improves functional outcome, if other conservative treatment modalities are ineffective. Viscosupplementation might delay the need for knee replacement surgery. Prospective study was conducted to know the efficacy of Viscosupplementation with hyaluronic acid (HA) in patients with osteoarthritis knee joint. 1200 patients meeting the inclusion and exclusion criteria with OA knee were included in the study. The patients were categorised based on radiological classification of Kellgren and Lawrence. Parameters includes Visual Analogue Scale (VAS) while performing activity of daily living modified the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index. We found that there is significant improvement in pain and functional outcome at 6 months of follow up. Here We came to a conclusion that intraarticular hyaluronic acid injection is potentially a effective treatment for osteoarthritis of knees in multiple doses and is adjunct treatment to oral analgesics to decrease the pain and its doses. It helps in improving the function in early osteoarthritis knee joint and might delay the need for future knee surgery

**Keywords-** Hyaluronic acid, Intraarticular Injections, Kellegren- Lawrence grade, Modified WOMAC Score, osteoarthritis knee (OA), VAS viscosupplementation.

### Introduction

Osteoarthritis (OA) is a clinical entity of joint pain with multifactorial etiopathogenesis and is characterized by the gradual progressive loss of articular cartilage, osteophyte formation, subchondral bone remodelling, and inflammation of the joint [i]. OA of knee is common problem in Indian population and happens to be a source of disability due to pain and loss of function, resulting in lost hours at work and difficulty in performing activity of daily living. It is one of the most common form of joint diseases, and is listed amongst top ten causes of progressive disability worldwide [ii]. With aging of the population, changes in lifestyle, diet changes and overweight, OA happens to be a major public health problem and presently poses a threat to financial burden worldwide and the incidence is rising rapidly [iii]. For the knee OA, various pharmacological and non- pharmacological treatment modalities are recommended by clinical guidelines regarding pain, disability and joint destruction [ii], [iv], [v].

Non-pharmacological modalities are important and includes patient education, exercises, weight reduction, sometimes walking with support (crutches) during acute phase, bracing of the knees, shoe modifications and modification of insoles to provide varus or valgus thrust to knee. Local heat and cold, massage, acupuncture, and electromagnetic therapy are also found to be helpful in subset of patients. Pharmacologic treatment is mainstay and includes mostly acetaminophen or paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), sometimes opioids, and drugs which slow down cartilage degeneration like glucosamine and chondroitin sulphate. These drugs which slow down cartilage degeneration are used in oral form, and are usually slow-acting drugs (glucosamine and chondroitin sulphate) and if orally administered, these drugs are usually not much effective. Intraarticular (IA) injection with corticosteroids, Hyaluronic acid (HA) and recently platelet rich plasma (PRP) is the last on list of non operative management. Intraarticular Hyaluronic acid (HA) has the ability of restoring normalization of synovial fluid viscoelasticity and also activates tissue repair process in articular cartilage [v],[vi].

### **Etiopathogenesis of OA**

Osteoarthritis of knee may be either primary (idiopathic) or secondary due to variety of reasons and could be secondary to trauma, resulting in joint incongruity and joint instability. The Hyaline cartilage of knee is the main target of harmful influences and subsequently causes osteoarthritis due to damage to the hyaline cartilage. The disease begins in hyaline cartilage and as the disease progresses it involves other structures within and outside the joint. Primary osteoarthritis usually starts at or just after middle age. Various causes apart from traumatic causes include - malalignment of knee due to any cause (varus/valgus), gouty arthritis, metabolic causes, endocrine abnormalities like gout, hyperparathyroidism and acromegaly.

There happens a progressive and ongoing breakdown of cartilaginous matrix and along with the inability of the reparative ability of hyaline cartilage, the dynamic equilibrium between is hampered and causes pain and results in inflammation. The cartilaginous matrix breakdown is regulated by an interplay of anabolic influences like Insulin like growth factors (IGF) I and II and catabolic influences like Interleukin (IL)I, Tumour necrosis factor (TNF) alpha and plenty of proteinases. To some extent, the anabolic and catabolic influence reduces or compensates for the harmful influences causing osteoarthritis. These influences also stimulate and modifies the chondrocyte metabolic activity. Whenever there is disturbance in the equilibrium of anabolic and catabolic influences and which exceed the body system's compensatory ability the matrix degradation occurs. This is the first step causing osteoarthritis of joints and if uncontrolled may progress to advanced disease causing pain and progressive disability (figure 1). The reason of cartilage degeneration is not yet well understood. Further, why in some patients there is more pain, despite early OA and in some patients there is less pain despite radiographic advanced disease is not well understood. The chondrocyte function impairment and matrix damage is also caused by enzymatic and mechanical factors.

*Matrix degeneration –progressive and accelerating => Repair and regeneration –attempt reduced ability =>Irreversible matrix degeneration starts => Loss of cartilage structure and hylan => Sclerosis / subchondral cysts / osteophytes => Malalignment / loss of congruence, deformity*

Flow diagram 1: Patho physiology of osteoarthritis of knee joint

### **Hyaluronic acid (ha) injection (Viscosupplementation)**

#### **Agents**

Hyaluronic Acid (HA) is produced from harvested rooster combs or from bacterial fermentation in vitro<sup>[vii]</sup>. The active ingredient is sodium salt of Hyaluronic acid, which is usually supplied as one prefilled 2ml (20 mg) syringe for

intraarticular use. The injectable hyaluronic products that are approved by FDA are sodium hyaluronate, Hylan G-F 20, and high-molecular weight hyaluronic acid. Injection schedules vary and usually are injected for almost 2 to 5 injections and patients are generally recommended to repeat the injection schedule at or after six month period, depending upon previous satisfaction and sufficient pain relief after the schedule of first injection. The scientific evidence in literature suggests that the use of low molecular weight hyaluronic acid and high molecular weight hyaluronic acid (HMWHA) have disease modifying effects due to the normalization of synovial fluid viscoelasticity and also due to activation of reparative process in articular cartilage. Further comparative clinical studies and meta-analyses favours the positive effects of HMWHA for knee OA [viii,ix]. However, because of lack of heterogeneity of studies, current literature is less conclusive or inconclusive. [x,xi,xii]

### **Mechanism of action**

Hyaluronic acid (HA) is a glycosaminoglycan which is naturally occurring and is a normal component of synovial fluid and the cartilage matrix. Moreover, cells from synovium, chondrocytes and fibroblasts synthesis the hyaluronic acid and then secrete it into the joint. Hyaluronic acid enhances the joint function due to normalization of synovial fluid viscoelasticity, and acts as a lubricant and also a shock absorber in nature during the different phases of joint movements [xiii,xiv]. It also has the ability reduces stress on hyaline cartilage and also tends to reduce friction on joint cartilage [xv]. Hyaluronic acid is also an important constituent of proteoglycans of the extracellular matrix. Hyaluronic acid also is postulated to be anti-inflammatory, mild analgesic and activates the tissue repair process of the articular hyaline cartilage [xvi].

### **Materials and Methods**

Present study was conducted in our hospital between January 2014 to January 2015 after getting approval of ethical committee. Total of 1200 patients were included in sample size who were suffering from symptomatic primary osteoarthritis of knee willing and consenting for intraarticular viscosupplementation of knee for three doses along with ability to follow up in osteoarthritis clinic were included in the study. Patients with post traumatic and other forms of secondary osteoarthritis were excluded from our study for the sake of uniformity. Patient who had recent history of effusion within a week time or presenting with effusion (hypertrophic osteoarthritis) of knee, any angular deformity of knee (varus and valgus), any contractures of knee and advanced osteoarthritis of knee at the time of enrolment were also excluded. The selected patients were administered three doses of hyaluronic acid injection in form intra articular 2 ml sodium hyaluronate (20 mg) at an interval of 7 to 10 days between each dose. The patients were categorised based on radiological classification of Kellgren and Lawrence. Data were collected from patients during the first visit at enrolment and follow-up visits at 7 - 10 days, 3 weeks, 3 months, and 6 months post-injection. Parameters includes VAS (visual analogue scale) score for pain ranging from 0 - 10 [xvii] and performance of activity of daily living (ADL). The Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index was modified according to the activity and need of Indian population and also taken into account at each of follow up. [xviii].

### **Radiographic evaluation**

After clinical examination, all patients were subjected to an anterior-posterior radiograph of knees and the osteoarthritis was graded using the Kellgren and Lawrence (KL) grading system, which classifies the osteoarthritis in one of five grades, with 0 representing normal and 4 representing the most severe. [xix]

**Results**

Data on 1200 patients who were injected all three doses of Hyaluronic acid intraarticular injections were evaluated in terms of demographic assessment, age, gender, occupation, adverse reaction due to injection, Bone Mass Index (BMI) severity of symptoms according to VAS and WOMAC. The data was followed up for 6 months and were analysed. During the pre injection phase all patients were subjected to Antero – Posterior standing radiographs of knee and graded according to classification based on Kellegren and Lawrence

**Adverse Effects –**

Most of the patients tolerated the injection procedure well. However 22 patients ( 1.8 %) complained of transient pain during or just after the injection procedure, lasting for 24 to 48 hours and subsiding thereafter.

The mean age was 52 ± 13.45 years. Among the 1200 subjects 56.66% (680/1200) were male and 43.44 % ( 520 /1200) were female.

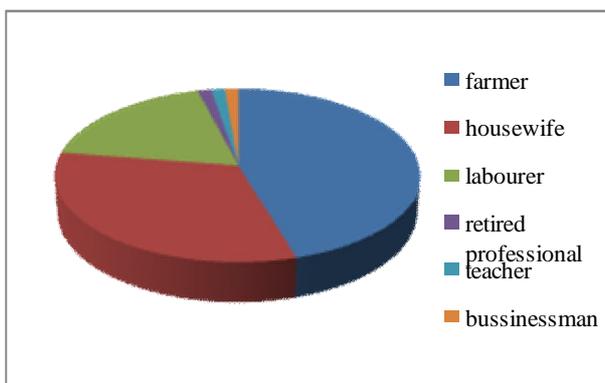


Figure 2: Occupation wise distribution of subjects

Left sided symptomatic Osteoarthritis was found in 41.66% (500/1200). Right was found in 58.33%(700/1200). Patients were studied according to Body Mass Index above and below 22 kg/m<sup>2</sup> and which was found to be significant.(p<0.05)

Table 1.Body Mass Index wise distribution of subjects

Chi Square Test		
BMI	No of patients	χ <sup>2</sup> -value
<22 kg/m <sup>2</sup>	466	7.89
>22 kg/m <sup>2</sup>	734	p value <0.05
Total	1200	

Table 2: Radiological grade wise distribution of subjects

K-L Grade	No of subjects	Percentage
0	0	0
I	508	42.33
II	724	52.33
III	61	5.08
IV	7	0.58
Total	1200	100

Table 2: Comparison of Mean Visual Analogue Score (VAS) e and Chair stand rate at baseline with 6 months follow up

Student paired t test						
Mean	baseline	Post injection Follow ups				p value
		10 <sup>th</sup> day	3 weeks	3 months	6 months	
VAS*	5.3	5.5	4.7	4.2	2.8	0.001
VAS- visual analogue scale.						

Table 3: Comparison of means of different component of modified WOMAC score at baseline and at 6 months follow up

Student paired t test						
Means	baseline	Post injection follow ups				p value
		10 th day	3weeks	3 months	6 months	
Pain	14	15	12	11	8	0.03
stiffness	6	4	5	5	5	0.62
Functional activity	62	50	42	40	38	0.04

## Discussion

Present study was done to assess the efficacy of intraarticular Viscosupplementation by Hyaluronic Acid (HA) in symptomatic osteoarthritis knee patients. The mean age of subjects with symptomatic OA knee was  $52 \pm 13.4$  years in our study. 56.33% subjects were male and 43.66% were female. In our study 80 % subject were involved in heavy day to day activities requiring frequent squatting and sitting cross leg. Our study had more subjects with right knee pain than left. 95 % Subjects in our study were having grade I and grade II osteoarthritis knee according to Kellgren and Lawrence radiological grading system. our Study showed the statistically significant improvement in VAS at 6 months follow up.(p value 0.01) According to Modified WOMAC score pain and functional activity showed statistically significant improvement (p value 0.03; p value 0.04 respectively) where as stiffness score was found to be insignificant. This showed that patient improved symptomatically and perform their day to day function with more comfort than previously. Joint stiffness remains there after injection may be due to diurnal variation, type of activity performed and seasonal changes. The pain and functional improvement in terms of VAS and modified WOMAC score was found to be more in patient with grade I and grade II OA knee while grade III and IV subjects were not benefited from the hyaluronic acid injection. Our mean age of subjects with OA was supported by the study of Pushpa S Patil<sup>[xx]</sup>, Harshal Salve<sup>[xxi]</sup>, Grace H. Lo<sup>[xxii]</sup>, Duygu Cubukcu<sup>[xxiii]</sup>, AMELA project<sup>[xxiv]</sup>. This strengthens the fact that development of primary osteoarthritis was increases with the age due to degenerative changes in the articular cartilage irrespective of their race and geographical representation. Our study results suggested that male are more predispose to OA knee which contradicts the study done by Pushpa S Patil<sup>[xx]</sup>, Duygu Cubukcu<sup>[xxiii]</sup>, which showed OA more common in female than male. This difference may be due to non uniform study groups. In our study correlation of BMI with symptomatic OA was found to be statistically significant.(p value<0.05). Similar results were found by M. S. Sridhar<sup>[xxv]</sup>. Hence overweight increases the symptoms in OA knee. Hence weight reduction with diet and exercise can be a way to reduce the symptoms. In our study intra articular HA injection showed better outcome in terms of pain and function in subjects with grade I and II while

Some studies comparing intra articular corticosteroid injection and NSAIDS with intraarticular hylauronic acid were done and found that both were equally effective [xxvi, xxvii]. Studies have questioned the efficacy of the treatment with HA. [xxviii],[xxix]. this may be due study design weaknesses and the enormous placebo effect in osteoarthritis clinical trials.

We concluded that OA is a disease of post 4<sup>th</sup> and 5<sup>th</sup> decade of life, mainly affecting the occupation involving more stress on knee joints. Symptoms of OA increases with increases in weight. Most of the subjects coming to hospital were in grade I and II of OA knee. 3 weekly doses of 2ml HA is found to be potentially effective in terms of symptomatic pain relief and functional outcome. This may also prolongs the need of total knee arthroplasty in patient with early OA. But long term study is needed to evaluate its role in cartilage regeneration. The cost of injection is also a major issue in India for the multiple doses over the NSAIDS, steroid and Platelet rich plasma intraarticular injections. The Hyaluronic acid (HA) injections had a good safety profile with fewer local reactions.

## References

- i . Martel-Pelletier J, Boileau C, Pelletier JP, et al. Cartilage in normal and osteoarthritis conditions. *Best Pract Res Clin Rheumatol* 2008; 22: 351-384 [DOI:10.1016/j.berh.2008.02.001]
- ii . National Collaborating Centre for Chronic Conditions (UK). Osteoarthritis: National clinical guideline for care and management in adults. London: Royal College of Physicians (UK), 2008.
- iii . Neogi T. The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis Cartilage* 2013; 21: 1145-1153 [DOI: 10.1016/j.joca.2013.03.018]
- iv . Jevsevar DS, Brown GA, Jones DL, Matzkin EG, Manner PA, Mooar P, Schousboe JT, Stovitz S, Sanders JO, Bozic KJ, Goldberg MJ, Martin WR, Cummins DS, Donnelly P, Woznica A, Gross L. The American Academy of Orthopaedic Surgeons evidence-based guideline on: treatment of osteoarthritis of the knee, 2nd edition. *J Bone Joint Surg Am* 2013; 95: 1885-1886 .
- v. Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P. OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage* 2010; 18: 476-499 [ DOI: 10.1016/ j.joca.2010.01.013]
- vi . . Kon E, Filardo G, Drobnic M, Madry H, Jelic M, van Dijk N, Della Villa S. Non-surgical management of early knee osteoarthritis. *Knee Surg Sports Traumatol Arthrosc* 2012; 20: 436-449 [DOI: 10.1007/s00167-011-1713-8]
- vii . McArthur BA, Dy CJ, Fabricant PD, Valle AG. Long term safety, efficacy, and patient acceptability of hyaluronic acid injection in patients with painful osteoarthritis of the knee. *Patient Prefer Adherence* 2012; 6: 905-910 .
- viii . Goldberg VM, Buckwalter JA. Hyaluronans in the treatment of osteoarthritis of the knee: evidence for disease modifying activity. *Osteoarthritis Cartilage* 2005; 13: 216-224.
- ix. Wang CT, Lin J, Chang CJ, Lin YT, Hou SM, et al. Therapeutic effects of hylauronic acid on osteoarthritis of the knee. A meta-analysis of randomized controlled trials. *J Bone Joint Surg Am* 2004; 86-A: 538-545 .
- x. Kotevoglou N, Iyibozkurt PC, Hiz O, Toktas H, Kuran B, et al. A prospective randomised controlled clinical trial comparing the efficacy of different molecular weight hyaluronan solutions in the treatment of knee osteoarthritis. *Rheumatol Int* 2006; 26: 325-330 .
- xi. Wobig M, Bach G, Beks P, Dickhut A, Runzheimer J, Schwieger G, Vetter G, Balazs E, et al. The role of elastoviscosity in the efficacy of Viscosupplementation for osteoarthritis of the knee: a comparison of hylan G-F 20 and a lower-molecular- weight hyaluronan. *Clin Ther* 1999; 21: 1549-1562 .

- xii. Divine JG, Shaffer MD. Use of viscosupplementation for knee osteoarthritis: an update. *Curr Sports Med Rep* 2011; 10: 279-284 [DOI: 10.1249/JSR.0b013e31822ed1b4]
- xiii. Maneiro E, de Andres MC, Fernández-Sueiro JL, Galdo F, Blanco FJ, et al. The biological action of hyaluronan on human osteoarthritic articular chondrocytes: the importance of molecular weight. *Clin Exp Rheumatol* 2004; 22: 307-312 .
- xiv. Brockmeier SF, Shaffer BS. Viscosupplementation therapy for osteoarthritis. *Sports Med Arthrosc* 2006; 14: 155-162.
- xv. Goa KL, Benfield P. Hyaluronic acid, et al. A review of its pharmacology and use as a surgical aid in ophthalmology, and its therapeutic potential in joint disease and wound healing. *Drugs* 1994; 47: 536-566 .
- xvi. Axe JM, Snyder-Mackler L, Axe MJ, et al. The role of viscosupplementation. *Sports Med Arthrosc* 2013; 21: 18-22.
- xvii. Lucile Packard Children's Hospital Heart Center/CVICU  
<http://www.pudendal.info/info/documents/ComparativePainScale.htm> - Author Alice Rich, RN – Recommender and Maintainer 12/08 Last Update
- xviii. <http://www.performanceptpc.com/paperwork/womac.pdf>
- xix. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthritis. *Ann Rheum Dis* 1957;16:494–501.
- xx. Patil pushpa, Department of Community Medicine, SDM College of Medical Sciences and Hospital ,Dharwad, India; Risk factors of Osteoarthritis Knee – A Cross-sectional study; ISSN: 2279-0853, ISBN: 2279-0861. Volume 2, Issue 5 (Nov.- Dec. 2012), PP 08-10.
- xxi. Salve Harshal , Junior Resident, Centre for Community Medicine, All India Institute of Medical Sciences, New Delhi, India; Prevalence of Knee Osteoarthritis amongst Perimenopausal Women in an Urban Resettlement Colony in South Delhi ; *Indian Journal of Public Health*, Volume 54, Issue 3, July-September, 2010
- xxii. Grace H. Lo; Associations of Varus Thrust and Alignment with Pain in Knee Osteoarthritis; *Arthritis Rheum.* 2012 July; 64(7): 2252–2259. doi:10.1002/art.34422.
- xxiii. Duygu Cubukcu, Relationships between Pain, Function and Radiographic Findings in Osteoarthritis of the Knee: A Cross-Sectional Study; *Arthritis* Volume 2012, Article ID 984060, 5 pages doi:10.1155/2012/984060.
- xxiv. F Navarro-Sarabia, 1 P Coronel, 2 E Collantes, 3 F J Navarro, 4 A Rodriguez de la Serna, 5 A Naranjo, 6 M Gimeno, 7 G Herrero-Beaumont, 8 et al on behalf of the AMELIA study group A 40-month multicentre, randomised placebocontrolled study to assess the efficacy and carryover effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: *Ann Rheum Dis* 2011;70:1957–1962. doi:10.1136/ard.2011.152017 1957
- xxv . Sridhar M.S.,C. D. Jarrett,J. W.Xerogeanes,S.et al A. Labib; Obesity and symptomatic osteoarthritis of the knee; *J Bone Joint Surg Br* 2012;94-B:433–40.
- xxvi Lo GH, LaValley M, McAlindon T, et al. Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis. *JAMA* 2003 ; 290 : 3115 – 21 .
- xxvii . Modawal A, Ferrer M, Choi HK, et al. Hyaluronic acid injections relieve knee pain. *J Fam Pract* 2005 ; 54 : 758 – 67 .
- xxviii. Wang CT, Lin J, Chang CJ, et al. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee. A meta-analysis of randomized controlled trials. *J Bone Joint Surg Am* 2004 ; 86-A : 538 – 45 .
- xxix .Arrich J, Piribauer F, Mad P, et al. Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: systematic review and meta-analysis. *Can Med Assoc J* 2005; 172 : 1039 – 43 .