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Intra articular hyaluronic acid injection, is it a wastage of money or justified?

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Abstract
Introduction: Osteoarthritis of knee (OA Knee) is one of the most common form of joint disease and affects everyone in different proportion with aging. To reduce the burden on society and improve the productive life various modalities of treatment are suggested. Our goal was to find out how much Intra Articular Hyaluronic acid injection (I/A HA inj.) is effective and safe.
Aim: To evaluate the Safety and efficacy of HA in proposed dosage.
Materials and Methods: We have done a retrospective single blind study on 60 patients of OA Knee according to ACR Criteria, Grade I and II, who were treated with I/A HA inj. Of a single brand. They were followed up to 3 year after last injection and clinical assessment done based on VAS Scale and WOMAC Score.
Results and Discussion: Out of 60 patients who have been given I/A HA injection, patients below age of 50 and ACR Grade I OA Knee, responded well with injection. However patients above age of 50 and ACR Grade II OA Knee responded poorly and requires some other form of treatment as early as 1 month after stopping injection.
Conclusion: Though OA Knee is a degenerative disease which requires long term follow up to justify use of I/A HA injection, We believe that in early cases of OA Knee and Patients below age of 50 years, this treatment modality can work well and may prolong active life and delay surgical intervention and hence cost benefit ratio justifies use of this treatment modality.

Keywords: Intra articular, hyaluronic acid, knee osteoarthritis

Introduction

Osteoarthritis (OA) is an important cause of chronic pain and disability worldwide among the elderly population [1]. OA is a very common problem in the older population and affects almost 5% of people over 65 years of age [2, 3, 4]. As population ages, disease progresses, it leads to deteriorating quality of life with pain, loss of mobility and functional independence. The general increase in life expectance means increase in number of people affected with OA. It affected more than 10 million people in India and there is increase in numbers by more than 8% annually and it's a major health problem worldwide. Osteoarthritis is the second most common rheumatologic problem and it is the most frequent joint disease with a prevalence of 22% to 39% in India [5, 6]. OA is more common in women than men, but the prevalence increases dramatically with age [5, 7, 8]. Nearly, 45% of women over the age of 65 years have symptoms while radiological evidence is found in 70% of those over 65 years [7, 8, 9]. OA of the knee is a major cause of mobility impairment, particularly among females [7, 8]. OA was estimated to be the 10th leading cause of nonfatal burden [7].

Osteoarthritis (OA) is a chronic degenerative disorder of multifactorial etiology characterized by the loss of articular cartilage, hypertrophy of bone at the margins, subchondral sclerosis, and range of biochemical and morphological alterations of the synovial membrane and joint capsule [5]. NSAIDS and glucocorticoids are the most common form of treatment in early stages and surgical intervention in end stage OA. However other modalities of treatment which aim at identifying causes of OA and treated the root cause are desirable.

Intra-articular injection of hyaluronic acid (HA) to treat OA has been used worldwide for pain relief and symptomatic treatment [10, 11]. The two types of HA currently available are low molecular weight (LMW) HA (molecular weight 0.5–3.6 million Da) and high molecular weight (HMW) chemically cross-linked HA (cHA, molecular weight 6.0 million Da) [12].

Hyaluronic acid is a very long polysaccharide chain, consisting of repeating disaccharide units of N-acetyl-glucosamine and glucuronic acid.

The average molecular weight of synovial fluid hyaluronic acid is 5 to 7 × 106 d, or 12,500 disaccharide units [13]. Endogenous hyaluronic acid is synthesized by type B synoviocytes and fibroblasts in the synovium and released into the joint space. Hyaluronic acid is a major component of synovial fluid and articular cartilage, and is an important contributor to joint homeostasis [13]. The viscoelasticity and rheology of synovial fluid is due entirely to its hyaluronic acid content. Hyaluronic acid contributes to the viscous and elastic properties, affording the synovial fluid the peculiar capacity to function differently under distinct loading conditions [14].

The normal adult knee contains approximately
2 mL of synovial fluid, with a hyaluronic acid concentration of 2.5 to 4.0 mg/mL [15]. In patients with osteoarthritis, the concentration and molecular weight of hyaluronic acid in synovial fluid is reduced by a factor of 2 or 3, owing to both degradation and dilution. Furthermore, the molecular weight of the hyaluronate that is present is reducedto as low as 2 × 105 d [13]. These consequences lead to dramatic changes in the viscoelastic properties of the synovial fluid, and, thus, altered joint mechanics. Decreased lubrication leads to increased stress upon the already diseased cartilage, further disrupting the collagen network and the integrity of the chondralsurface [15].
Intra Articular HA injection weekly for 3 to 5 weeks has been shown to increase joint performance in short and medium term in various studies owing to viscoelastic properties.

Aim: To evaluate the Safety and efficacy of HA in proposed dosage.

Materials and Methods
The study was carried out at Harikrishna hospital, Dholka, Ahmedabad. The study was carried out from November 2012 to November 2013 and patients were followed upto a maximum duration of 3 years. This study was a retrospective single blind randomized study, consisting of two groups. One group given intraarticular placebo and second group given intra articular HA injection. All other treatment modalities were same including supportive analgesics, physiotherapy and life style modification.
The following were the inclusion and exclusion criteria:
Inclusion criteria: All patients between the age of 30 to 75 years, radiographic evidence of the osteoarthritis of knee joint, chronic pain for atleast 3 months prior to entry in the study, not satisfied with previous non operative management.
Exclusion criteria: Osteoarthritis > stage 3, any intraarticular injection in the previous 3 months, allergy or hypersensitivity to any of the study medication, history of any crystalline arthropathy, inflammatory arthritis or neuropathic arthropathy.
Total 5 doses of I/A HA injection were given at weekly intervals and patients were called for follow up at 3 month, 6 month, 1 year and 2 years. Evaluation was based on VAS Scale [16] and WOMAC Score [17]. End result was also assessed clinically by independent blind examiner.
Although an intra-articular injection of the knee is not a complex procedure, assessment of whether the tip of the needle lies free in the joint or is embedded in synovium or soft tissue before administration of the preparation of medication could be difficult. This finding emphasizes the importance of proper needle placement. Needle placement is easily confirmed when an effusion is present. The return of synovial fluid documents intra-articular placement of the needle. In the absence of an effusion, needle placement requires the use of anatomic landmarks and tactile feed-back to help the operator in positioning of the needle. Prior to performance of an injection, all landmarks for entry into the joints were outlined with a marking pen. After palpating the lateral and medial borders of the patella The needle was advanced transversely between the articular surfaces of the patellofemoral joint at the midpoint of the patella. After the completion of data collection, data entry and analysis was done by Excel 3.0.

Results
Out of 60 patients enrolled, 39 were female and 21 were male patients. Average of female patients was 54 yrs (range from 40-75), and male patients was 59 yrs (range from 41-75). 31 patients were grade I OA knee, 19 patients were grade II OA Knee and 10 patients were grade III OA Knee as per ACR Criteria [18].

Table 1: Study epidemiology.

Male	21
Female	39
Total	60

Table 2: ACR grading.

ACR grade	Number of patients
1	31
2	19
3	10

There is statistically significant difference in VAS Scale and WOMAC Score in Grade I OA Knee patients irrespective of Age and Sex. Where as Grade II patients responded with moderate improvement. In patients with grade III OA Knee, or patients more than 50 years of age, the response was poor and in fact at 6 month follow up most of the patients were dissatisfied with treatment and asked for change of modality of treatment.

Table 3: Clinical improvement on follow up.

	VAS Scale	Womac Score
Grade I	Significant improvement	Significant improvement
Grade II	moderate	Moderate
Grade III	poor	Poor

In grade I OA Knee patients the improvements were consistent in most of the patients upto 2 years follow up with proper modification of lifestyle, physiotherapy and education. Some patients of OA Knee worsened over 2 year follow up. In few patients post injection joint swelling and discomfort was seen for few days, however no infection or any other complication encountered.
Average cost of therapy was 9000/- patient and patient were happy with cost benefit ratio, considering activity they were able to do post injection and improvement in their Knee function.

Discussion
As we have stated our main objective elsewhere, we believe OA Knee is a age related degenerative disorder likely to occur in most of human with advancing age and most of the people want to avoid surgery as far as possible considering restriction of life style and cost involved in surgery and post surgical care. Current pharmacological, non-pharmacological, and surgical treatments for OA can alleviate some symptoms, but do not attenuate disease progression. Drugs, such as glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDs), have been widely used for the treatment of OA; however, none of the current

drugs can prevent cartilage degeneration or completely cure this intractable disease. Furthermore, many of the drugs are not ideal for long-term treatment because of some adverse effects In addition, delaying a primary surgery means to prevent a second surgery in form of revision surgery which involves huge cost and results are inferior as compare to primary replacement surgery with increased complications.

In the previous trial of Bellamy comparing IA HA injections with IA corticosteroids, there were no significant differences 4 wk after injection but IA HA was more effective 5-13 wk post injection [19, 20]. A meta analysis of seven randomized control trials done by Bannuru also showed that intra articular injection of hyaluronic acid is better than intra articular corticosteroids in patients of osteoarthriris knee [21]. In the first two weeks, corticosteroids were more effective in relieving pain, but at week 4, both were equally effective, and from week 8, HA was more effective to last assessment at 26th week. Analyses of the results for other outcomes such as reduction in stiffness and improvement in function following IA HA were similar.

As intra articular HA is only outdoor procedure and not associated with significant complication, patient compliance was very good. Patients with early osteoarthritis are likely to benefit most as in them wear and tear or cartilage has just started and hence activity modification and intraarticular HA likely to have most beneficial effect on them.

HA is a primary component in synovial fluid and articular cartilage matrix. The maintenance of normal joint function is tightly correlated with a normal concentration of HA in the synovial fluid [22]. Intra-articular injection of HA can cover the articular surfaces and improve nutrient transport in cartilage, acting as a cushion that absorbs pressure and friction, thus protecting it from further damage. The adherence of HA to knee articular cartilage surfaces has been reported to protect nerve endings that may be exposed by cartilage degradation [23, 24]. Intra-articular treatment with HA for OA knee pain is widely accepted in clinical practice [13]. This method can supply sufficient HA to delay the development of knee OA.

Conclusion

When treating a patient with osteoarthritis, it is best to start with non-interventional approaches, such as physiotherapy, ice, and analgesics. If conservative treatment fails, injectable agents may help. Hyaluronic acid injections provide longer-lasting pain relief than corticosteroids for patients with osteoarthritis; however, they are much more expensive. Different modalities of intra articular injections are being investigated like growth hormone, platelet rich plasma and autologous blood transfusion but these are still under research and documented results are still not conclusive.

However there are limitations of our study. Ours is a short-term study and as OA is an age related degenerative disorder, we need to follow up this patients for longer term. Long term follow up of at least 5 years on larger population is required however to use I/A HA Injection on mass scale basis which can further reduce it's cost and improve upon cost benefit ratio. It needs to be quantified that over longer term follow up how many persons have been able to avoid surgery or delay surgery. As advanced OA knee patients were not having desired results for them option is only surgery and hence no true cost benefit ratio for them, who are actually in need of surgery and hence I/A HA injection can't be called as substitute for any other surgical intervention.

However over longer term if some screening test is developed for OA Knee and population at high risk can be treated with this modality in early stage OA and can be beneficial over longer term.

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