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Comparison of intra-articular steroid injection and hyaluronic acid in mono-articular synovitis knee

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Abstract
Introduction: Mono articular presentation of rheumatoid arthritis is infrequent and has been previously reported to involve the hip and knee joints. Rheumatoid arthritis is a common symmetrical chronic inflammatory arthritis with the prevalence of 1% worldwide. Mono- articular rheumatoid arthritis is a rare entity reported to initially affect large joints such as hips and knees, progressing to a poly articular presentation within 3 to 5 years. Synovitis is an important component of rheumatoid arthritis, so we conducted a study to include all the recurrent effusion of knee cases, and we have compared the functional outcome of intra-articular steroid injection and hyaluronic acid in the treatment of such cases.
Material and Methods: 40 cases of recurrent effusion of knee joint attending the OPD or emergency services at Government Medical College and Rajindra hospital, Patiala between July 2016 to July 2019 were evaluated with the clinical examination, haematological investigations and radiological investigations. In all the cases, the joint was aspirated with a 16 G Needle and aspirated fluid was sent for pus cultural sensitivity in a microbiology Department of our hospital and was sent for CBNAAT to chest and TB hospital of our hospital. In Group 1, following the aspiration, injection of local corticosteroid (methylprednisolone acetate 80 mg) was given and in group 2, injection of hyaluronic acid was given, followed by a short course of antibiotics for 5 days and short course of non-steroidal anti-inflammatory drugs was given for 10 days and a crêpe bandage was applied for 2 days. The results were assessed by VAS for pain and KOOS (Knee Injury and Osteoarthritis Outcome Score) scores.
Results: In all 40 patients, the pus cultural sensitivity was negative for any microorganism and CBNAAT was negative in all the 40 patients. By comparing the results obtained in KOOS scale it was seen that symptoms improved after six months in both steroid (P = 0.017) and HA groups (P = 0.004). Besides, daily activity improved in both steroid (P = 0.027) and HA groups (P = 0.047). On the contrary, pain did not decrease 6 months after intervention in both steroid (P = 0.096) and HA groups (P = 0.17)
Conclusion: Mono articular synovitis in an otherwise seronegative patient is due to recurrent inflammatory response due to recurrent stress or any other intra articular pathology.
Patients are advised rest, and a short course of steroidal anti-inflammatory drugs, which also helped to relieve the inflammation. This was markedly improved by intra-articular HA injection as shown by the recovery in intra-articular HA injection group as compared to the steroid group.

Keywords: Intra-articular injection, Hyaluronic acid, Methylprednisolone acetate

Introduction
Mono articular presentation of rheumatoid arthritis is infrequent and has been previously reported to involve the hip and knee joints. Rheumatoid arthritis is a common symmetrical chronic inflammatory arthritis with the prevalence of 1% worldwide [1]. Untreated rheumatoid arthritis can result in both short and long-term complications with an increase in mortality and morbidity. A large US cohort reports that 35% of patients with RA had a disability, 10 years after diagnosis [2]. The initial American College of rheumatology classification criteria for RA have been recently updated to increase the sensitivity to diagnose early RA and enable early intervention [3]. The 2010 ACR/EULAR criteria for definite RA consist of a point-based system that includes 4 domains: confirmed synovitis in at least one joint (higher scores are assigned by a higher number of small joints involved) (0-5), presence of RA antibodies (rheumatoid factor {RF}) and anti-cyclic citrullinated peptide antibody (anti-CCP) (0-3), elevated acute phase reactants (CRP), and erythrocyte sedimentation rate (ESR) (0-1) and

symptom duration of 6 weeks or longer (0-1) [4]. The presence of symmetrical poly arthritis and morning stiffness had been included in the 1987 criteria. These manifestations have not been found to be significantly important for the purpose of data analysis in the phase 1 2010 ACR/EULAR criteria [3, 5]. Mono- articular rheumatoid arthritis is a rare entity reported to initially affect large joints such as hips and knees, progressing to a poly articular presentation within 3 to 5 years [6, 7]. As synovitis is an important component of rheumatoid arthritis, so we conducted a study to include all the recurrent effusion of knee cases, and we have compared the functional outcome of intra-articular steroid injection and hyaluronic acid in the treatment of such cases

Material and Methods

40 cases of recurrent effusion of knee joint attending the OPD or emergency services at Government Medical College and Rajindra hospital, Patiala between July 2016 to July 2019 were evaluated with the clinical examination, haematological investigations and radiological investigations. Inclusion criteria were recurrent swelling and effusion in either of the knee joint in otherwise afebrile patient with no history of trauma and no small joint involvement. Exclusion criteria were patients having small joint involvement and morning stiffness or history of fever or history of weight loss or loss of appetite. They were then randomly allotted in two groups. On the presentation, detailed history was taken to see the number of joints involved and to check for timing of effusion and history of previous aspirations, if any. A detailed and meticulous clinical examination was performed, including patellar tap. Haematological investigations ordered for all the patients were complete hemogram, fasting acute phase reactants (ESR, CRP), were performed and was checked for presence of Rheumatoid factor and anti-cyclic citrullinated peptide antibody (anti-CCP). Plain radiography of knee joint was done in all cases and MRI was done in selected cases.

In all the cases, the joint was aspirated with a 16 G Needle and aspirated fluid was sent for pus cultural sensitivity in a microbiology Department of our hospital and was sent for CBNAAT to chest and TB hospital of our hospital. In Group 1, following the aspiration, injection of local corticosteroid (methylprednisolone acetate 80 mg) was given and in group 2, injection of hyaluronic acid was given, followed by a short course of antibiotics for 5 days and short course of non-steroidal anti-inflammatory drugs was given for 10 days and a crêpe bandage was applied for 2 days. The results were assessed by VAS for pain and KOOS (Knee Injury and Osteoarthritis Outcome Score) scores.

The Knee Injury and Osteoarthritis Outcome Score (KOOS) is designed to evaluate the patients' attitude on the knees and related problems, the KOOS is a tool specifically used for knee. The KOOS measures not only short-term but long-term sequellae of knee injury. It contains 42 items in 5 scored subscales including Pain, Other Symptoms, Function in daily living (ADL), Function in Sport and Recreation (Sport/Rec), and Knee-related Quality of Life (QOL).

Visual analog scale

The visual analog scale (VAS) is an instrument regularly used to measure pain intensity based on a 0–10 cm. In the present study, the researcher asked the patients: "Based on VAS, how much pain are you in/experiencing?" In the follow-up sections, based on VAS, the researcher asks about their pain again. The measurement was recorded by the orthopedic surgeon.

Procedure

Patient is made to lay down in supine position with the affected knee exposed to the groin area. Part is painted and draped. Under sterile conditions, local anaesthetic is instilled into the skin at the port of entry, which is in superolateral part of the knee. After that, the fluid is aspirated from the superolateral pouch and part of the fluid is sent for pus cultural sensitivity and part of the fluid is sent for CBNAAT testing, as described above. After that, through same portal an injection of 80 mg of methyl prednisolone acetate is injected in one group and injection of hyaluronic acid is injected in the other group. Following which a sterile dressing is applied for 2 days and a crêpe bandage is applied over that. Patient is advised to give rest to the part for 7 days, along with the course of non- steroidal anti-inflammatory drugs for ten days. Patients were reviewed for follow up at 1 week, 1 month, 2 months and 6 months.

Mechanism of action

Corticosteroids have both anti-inflammatory and immunosuppressive effect, but their mechanism of action is complex. Corticosteroids act directly on nuclear steroid receptors and interrupt the inflammatory and immune cascade at several levels. By this means, they reduce vascular permeability and inhibit accumulation of inflammatory cells, phagocytosis, production of neutrophil superoxide, metalloprotease, and metalloprotease activator, and prevent the synthesis and secretion of several inflammatory mediators such as prostaglandin and leukotrienes [8]. The clinical anti-inflammatory reflections of these actions are decreases in erythema, swelling, heat, and tenderness of the inflamed joints and an increase in relative viscosity with an increase in hyaluronic acid (HA) concentration [9].

Hyaluronic acid (HA) is a naturally occurring glycosaminoglycan and a component of SF and cartilage matrix. Synovial cells, fibroblasts and chondrocytes synthesize HA and secrete into the joint. HA enhances viscosity and elastic nature of SF. SF with normal HA concentration acts as a viscous lubricant during slow joint movements and as an elastic shock absorber during rapid joint movements [10]. The IA injection of HA is thought to restore normal viscoelastic properties of the pathologically altered SF, which explains the term of the approach: "viscosupplementation". It is thought that HA temporarily restores the lubricating and shock-absorbing effects of SF [11].

Results

In all 40 patients, the pus cultural sensitivity was negative for any microorganism and CBNAAT was negative in all the 40 patients. None of the patient had history of weight loss, low-grade fever, and evening rise of temperature. In 20/40 patients, hemoglobin was found to be less than 10, accounting for malnutrition in India. TLC /DLC was within normal range in all the patients.

22 patients were males and 18 patients were females. All the patients were having unilateral involvement. Rheumatoid factor was negative in all the patients and anti-CCP was negative in all the patients.

Out of 20 patients in intra-articular steroid injection group, 17 patients did not have effusion, even at follow-up at 6 months, 2 patients had no effusion at two-month follow-up, but had effusion at six-month follow-up. One patient had effusion even at one month follow up. Out of 20 patients in hyaluronic acid group, 10 patients did not have effusion, even at follow-up at 6 months, 3 patients had no effusion at two-month

follow-up, but had effusion at six-month follow-up. 7 patients had effusion even at one month follow up.

At the start of study, pain score in steroid group was same as HA group with insignificant p-value. In corticosteroid group, pain at end of first month significantly decreased to 5.58 ± 2.47 (P < 0.001). At the end of second month, pain increased to 5.83 ± 2.21 but it was significantly lower than pain before intervention (P < 0.001). At end of sixth month, pain score increased to 6.39 ± 2.07 and it was not statistically different with primary pain (P = 0.200). In HA group at end of first month, pain significantly decreased to 6.59 ± 2.01 (P < 0.001). At end of second month, pain continued its decreasing trend to 6.39 ± 2.04 (P < 0.001). At end of sixth month, pain score increased to 6.64 ± 2.01 but it was also significantly lower than primary pain (P = 0.021). The difference of pain between two groups was significant at end of first month (P = 0.017), but it was not significant at the end of second (P = 00.16) and sixth month (P = 0.728)

By comparing the results obtained in KOOS scale it was seen that symptoms improved after six months in both steroid (P = 0.017) and HA groups (P = 0.004). Besides, daily activity improved in both steroid (P = 0.027) and HA groups (P = 0.047). On the contrary, pain did not decrease 6 months after intervention in both steroid (P = 0.096) and HA groups (P = 0.17).(Table 1)

Table 1: Comparision of KOOS Scores between the two study groups

Koos Scores	Steroid	HA	p-value
Pain before (0–100)	34.99	31.48	0.328
Pain after (0–100)	37.95	34.74	0.383
Symptoms before (0–100)	39.23	40.19	0.784
Symptoms after (0–100)	43.78	46.20	0.473
Daily activities before (0–100)	47.08	47.20	0.970
Daily activities after (0–100)	51.04	50.67	0.867

Discussion

Synovial inflammation plays an important role in the symptoms of monoarticular knee. Soluble inflammatory mediators, such as cytokines and chemokines, are increased in synovial fluid and promote synovitis [12]. Recent histological researches demonstrated that synovitis occurs even in early stages of disease, but the prevalence of synovitis increases with advancing disease stage [13]. The cause of synovial inflammation is still unclear but hypothesized either as a result of foreign body reaction of synovial cells to degraded cartilage products inside the joint [14].

Intra-articular steroid injections are frequently used to treat acute and chronic inflammatory conditions. From randomized controlled trials in OA patients there is evidence that intra-articular steroids are effective, but their benefit over placebo may be relatively short-lived, up to four weeks. In a 2006 Cochrane Review, the short term efficacy of corticosteroids in knee OA has been confirmed [15], and recently, the short-term effect was also highlighted in a systematic review by Hepper *et al.* [17] and in a meta-analysis by Bannuru *et al.* [27]. A study by Chao *et al.* also found intra-articular steroids to be superior to placebo on Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total subscale scores at four weeks [18].

It is believed that HA temporarily restores the lubricating and shock-absorbing effects of synovial fluid. Moreover, several studies suggest that viscosupplements also have disease modifying effects, such as reduction of synovial inflammation [19], protection against cartilage erosion, and promotion of intra-articular hyaluronic acid production. However the precise in vivo mechanisms of action are poorly known in the joint [20]

However, despite many clinical trials, the efficacy of HA is a matter of debate with markedly discordant interpretations of the data [21]. Among the published meta-analyses, two concluded an overall beneficial effect for HA injections, four reported a small benefit, and two found no evidence to support HA injection therapy [22]

The inconsistent results reported in meta-analysis and guidelines are mainly due to the adoption of different inclusion and exclusion criteria, leading to some papers to be included in certain meta-analysis and excluded from others. Furthermore, heterogeneity, methodological errors, and confusion on effect size interpretation have also been reported [23].

By using VAS and KOOS scales, it was shown that both medications were equally effective in pain reduction at the end of first and second month after intervention. The effectiveness of pain reduction was more durable in HA group compared to CS. This was like what previous studies also provide [24]. At the end of the sixth month, pain score increased after decreasing at first and second month endpoints. At this point the score was not statistically different with the primary pain prior to intervention. It could be concluded that the duration of pain relief effectiveness is less than 6 months. On the contrary, the pain score remained significantly low after 6 months. In other words, the durability of efficacy of HA is more than 6 months and significantly longer compared to CS. These results are similar to the findings obtained by Leighton *et al*., who reported the more durable effectiveness of HA compared to methylprednisolone [25]. Similar results were also noted by Askari *et al.* [26].

Conclusion

Mono articular synovitis in an otherwise seronegative patient is due to recurrent inflammatory response due to recurrent stress or any other intra articular pathology.

Patients are advised rest, and a short course of steroidal anti-inflammatory drugs, which also helped to relieve the inflammation. This was markedly improved by intra-articular HA injection as shown by the recovery in intra-articular HA injection group as compared to the steroid group.

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