Intra-Articular Ozone Therapy in Osteoarthritis of Knee in Reducing Pain and Improving Function in a Tertiary Care Hospital in North-East India: A Randomized Controlled Study

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Abstract: Osteoarthritis (OA) is a chronic disorder of synovial joints in which there is progressive softening and disintegration of articular cartilage accompanied by new growth of cartilage and bone at the joint margins, cyst formation and sclerosis in the subchondral bone, mild synovitis and capsular fibrosis. According to World Health Organization (WHO), osteoarthritis is the second commonest musculoskeletal problem in the world and affects 30% of the population after back pain (50%). WHO estimates that osteoarthritis affects 9.6% of men and 18% of women older than 60 years of age. Knee joint involvement is typically associated with pain on descending or ascending stairs, squatting, climbing into rickshaws, buses, etc. Signs of OA knee include bony swelling, crepitus, restricted movement, deformity of knee joint, muscle weakness and muscle wasting. Recently, intra-articular injection of ozone-oxygen mixture in therapeutic concentration (30 micro g/ ml of ozone in oxygen) gained popularity for relief of pain, and physical disability without any significant adverse effect. Only a few literatures on management of OA knee with ozone therapy in North-East India is available out of the many studies that have been conducted so far.

OBJECTIVE: To assess the effectiveness of intra-articular ozone therapy in osteoarthritis of knee in reducing pain and improving function in a tertiary care hospital in North-East India.

METHOD: Seventy patients with OA knee were randomly allocated to 2 groups (Group A and B). Group A (n=30) received intra-articular ozone therapy while Group B (n=30) received paracetamol with exercise. Visual Analogue Scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) were used as outcome measures.

RESULTS: Mean VAS score was 7.91±0.942 at baseline, which improved to 4.43±0.608 at first month and 1.92±0.702 at third month. The WOMAC score in ozone group was 85.94±4.051 at baseline, which improved to 40.77+6.847 at 1st month and 15.26±2.267 at 3rd month. The findings in both groups were statistically significant ($p<0.001$).

CONCLUSION: Intra-articular ozone therapy was effective for pain relief and functional improvement in Kellgren-Lawrence (KL) grade 2 and 3 OA knee in the first 3 months after injection.

Index Terms: Osteoarthritis, ozone, VAS, WOMAC

I. INTRODUCTION

Osteoarthritis (OA) is a chronic disorder of synovial joints in which there is progressive softening and disintegration of articular cartilage accompanied by new growth of cartilage and bone at joint margins, cyst formation and sclerosis in subchondral bone, mild synovitis and capsular fibrosis.[1] OA can be 'primary' when there is no antecedent factor and 'secondary' when it occurs following acute or chronic trauma, connective tissue diseases, endocrine or metabolic diseases, infection, crystal deposition and bone dysplasias.[2] According to World Health Organization (WHO), OA is the second commonest

musculoskeletal problem in the world (30%) after back pain (50%).[3] WHO estimates that OA affects 9.6% of men and 18 % of women older than 60 years.[4] The prevalence of osteoarthritis in India is 22% to 39%.[5] The major risk factors associated with osteoarthritis knee are female gender, obesity, occupational knee bending, physical labour, metabolic diseases like diabetes, fluorosis and chondrocalcinosis.[3] The articular cartilage is devoid of nerve endings, hence the pain in osteoarthritis originate from other structures like stretching of nerve endings in periosteum covering osteophytes, joint instability, stretching of joint capsule or ligaments, synovitis and muscle spasm. Synovitis in osteoarthritis may be due to phagocytosis of shards of cartilage and bone from abraded joint surface. In other cases, immune complexes, containing antigens derived from cartilage matrix may be sequestrated in collagenous tissues of the joint, leading to low grade synovitis.[6]

The cardinal symptom of osteoarthritis knee is pain in and around the joint. Knee joint involvement is typically associated with pain on descending or ascending stairs, squatting for toilet, climbing into rickshaws, buses, private vehicles, etc. Signs of OA knee include bony swelling, crepitus, restricted movement, deformity of knee joint, muscle weakness and muscle wasting. Occasionally, the knee show signs of inflammation and effusion.[3] Laboratory tests may be done to rule out metabolic arthropathy like gout and inflammatory arthritis. Analysis of synovial fluid in OA reveals a WBC count of less than 2000/cumm with mononuclear cell predominance, without any crystals.[7] Standard radiographs are the most common investigations in osteoarthritis knee, which is best demonstrated in weight bearing X-rays. The earliest feature is joint space narrowing, and it is also used as a measure of progression of osteoarthritis knee. Osteophytes, subchondral bone sclerosis, subchondral cysts, deformity, loose bodies and calcification are the other changes. Ultrasound is useful in assessing changes in periarticular structures like Baker's cyst. MRI is rapidly developing into a tool for evaluation of cartilage in osteoarthritis.[3] Radiological disease progression is measured by Kellgren-Lawrence (KL) Score [Table 1].[8]

Table 1: Kellgren-Lawrence (KL) Score

Grade 1	Possible osteophytes Doubtful narrowing of joint space
Grade 2	Definite osteophytes Definite narrowing of joint space
Grade 3	Multiple osteophytes Definite narrowing of joint space Some sclerosis Possible deformity of contour
Grade 4	Large osteophytes Marked narrowing of joint space Severe sclerosis Definite deformity of bone contour

The goals of osteoarthritis management are to decrease pain, improve function in activities of daily living (ADL), prevent and correct deformity, and slow down the progression of disease. Among non-pharmacological measures, patient education about the disease and joint protection measures like avoidance of squatting, prolonged standing, climbing stairs, limitation of excess joint loading by weight reduction are important. Isometric strengthening exercises of quadriceps, hamstring hip extensors and abductors are encouraged. Orthotic shoes, knee braces and walking aids like canes, crutches, when used properly lead to pain relief with improved function.[3] Pharmacological measures include acetaminophen and selective COX-2 inhibitors like meloxicam, celecoxib, etoricoxib, etc.[6] Intra-articular steroids are given if there is evidence of acute inflammation and joint effusion. A maximum of three intra-articular steroid injections can be given in the same joint. Surgical measures include osteotomy, arthroplasty,

synovectomy, loose body removal, debridement,etc with varying grades of efficacies.[3] Recently, intra-articular injection of ozone-oxygen mixture (0_3-0_2) in therapeutic concentration (30 micro g/ ml of ozone in oxygen) gained popularity for relief of pain, ssstiffness and physical disability without any significant adverse effect. Ozone referred to as O_3, is the triatomic state of oxygen. It is colourless, pungent in odour, explosive in liquid or solid form and has a half-life of 20 minutes only. Increase in temperature decreases its half-life.[9] Corona discharge, ultraviolet and cold plasma generators are the main types of ozone generators. Ozone is gradually gaining popularity in various medical fields especially in pain management. This study was conducted since there is no literature on OA knee management with ozone therapy in North-East India. Moreover, the population of North-East India usually carry out daily activities at floor level thereby, increasing the chances of developing osteoarthritis. So we have taken up this study to find out the effectiveness of intra-articular ozone in OA knee for pain control and functional improvement.

II. MATERIALS AND METHOD

A randomized controlled study on 70 patients with knee pain attending the Department of Physical Medicine and Rehabilitation, Regional Institute of Medical Sciences (RIMS), Imphal, India, was conducted from October 2014 to April 2016. Approval from the Research Ethics Board, RIMS, Imphal was taken before starting the study and written informed consent was obtained from all subjects.

Patients with primary OA of KL grade 2 and 3 aged 51-70 years with BMI < 30 who were willing to co-operate and give consent with no other medical or neurological complications were included in the study. However, patients with secondary OA, metabolic disease of bone and inflammatory joint disease were excluded from the study.

Randomization was done using block of four methods.

Patients enrolled in the study were assigned to two groups, A and B [Table 2].

Group A (intervention group) received 10ml of intra-articular ozone with tablet Paracetamol 500mg twice a day and isometric quadriceps and hamstrings strengthening exercise while, Group B (study group) received Paracetamol and exercise.

Study variables were age, gender, BMI, occupation and side of affection.

Table 2: Baseline characteristics of patients in ozone and Paracetamol groups

Variables	**Study Group (Ozone) N (%)**	**Control Group (Paracetamol) N (%)**	**p – value**
Mean Age	62.11±5.48	64±5.19	p > 0.05
Gender			
Male	13(37.1)	22(62.9)	
Female	22(62.9)	13(37.1)	
Occupation			
Housewife	16(45.7)	19(54.3)	
Business	5(14.3)	6(17.1)	
Teacher	9(25.7)	6(17.1)	
Farmer	5(14.3)	4(11.4)	
BMI			
Normal	11(31.4)	14(40)	
Obesity Grade 1	24(68.6)	21(60)	
Site Of Affection			

Right	15(42.9)	16(45.7)	
Left	1(2.9)	0(0.0)	
Both	19(54.3)	19(54.3)	

The baseline characteristics of the two groups had no significant differences with p value more than 0.05. Study tools included a pre tested proforma, X- ray of both knees in standing (AP view) and Medical Ozone Generator: Chemotronics, Made in India (Model No: MD/OG-60S). Release of pungent smell and perforation of gloves were used to confirm the generation of ozone.

Pain measured by Numerical Visual Analogue Scale (VAS) and functional disability measured by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) were the outcome measures.

In ozone group (intervention group) patients were placed in supine position with knee(s) at the edge of table in flexion. Proper aseptic and antiseptic measures were taken. Joint fluid if present, was aspirated. After localizing the patella, a 21G needle was inserted using the infero-lateral approach and 10ml of ozone was injected slowly. Then routinely, ten repetitions of passive flexion-extension movements of the knee were done to distribute ozone throughout the joint.

Assessments were done at baseline, 1st and 3rd month.

III. STATISTICAL ANALYSIS

Data analysis was performed by Statistical Package for Social Sciences (SPSS) version 21. For descriptive data, mean and standard deviation were used. For calculating the significance of the study, paired "t" test was used. For comparing between means, Analysis of Variance (ANOVA) was taken into consideration and $p < 0.05$ was taken as level of significance.

IV. RESULTS

There were no significant differences in baseline characteristics of the two groups in pain, functional ability and medication use and hence were comparable. The mean age of patients was 62.11±5.48 in the intervention group out of which 13(37.1%) were males and 22(62.9%) females and 64.63±5.19 in the control group of which 22(62.9%) were males and 13(37.1%) females. The pain intensity as measured by VAS score showed significant reduction at the follow up periods in ozone group. The mean VAS score was 7.91±0.942 at baseline, which improved to 4.43±0.608 at the first follow up and 1.92±0.702 at second follow up [Table 3].

Table 3: Repeated measures ANOVA for differences in VAS score over time between the groups (n=70)

Group	**VAS at baseline Mean (SD)**	**VAS at 1st month Mean (SD)**	**VAS at 3rd month Mean (SD)**	**Effect Size**	**p value**
Ozone	7.91(0.74)	4.43(0.61)	1.92(0.70)	0.05	<0.001
Paracetamol	7.00(0.73)	5.23(0.91)	5.34(0.80)		

The effect size of change in pain as measured by VAS scores over time between the two groups was 0.05 and was found to be statistically significant (p=0.001) [Table 3].

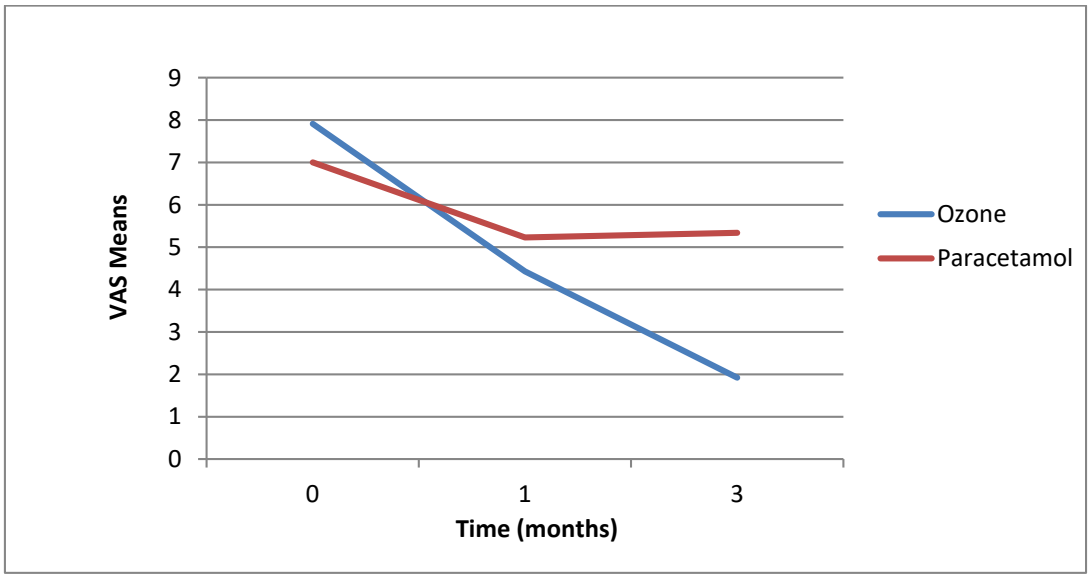

Figure 1: A graph plot of the mean VAS scores from baseline to 3rd month of follow up

Table 4: Repeated measures ANOVA for differences in WOMAC score over time between the groups (n=70)

Group	WOMAC at baseline Mean (SD)	WOMAC at 1st month Mean (SD)	WOMAC at 3rd month Mean (SD)	Effect Size	p value
Ozone	85.94(4.05)	40.77(6.85)	15.26(2.26)	0.252	<0.001
Paracetamol	70.80(5.84)	45.80(9.35)	45.23(9.22)		

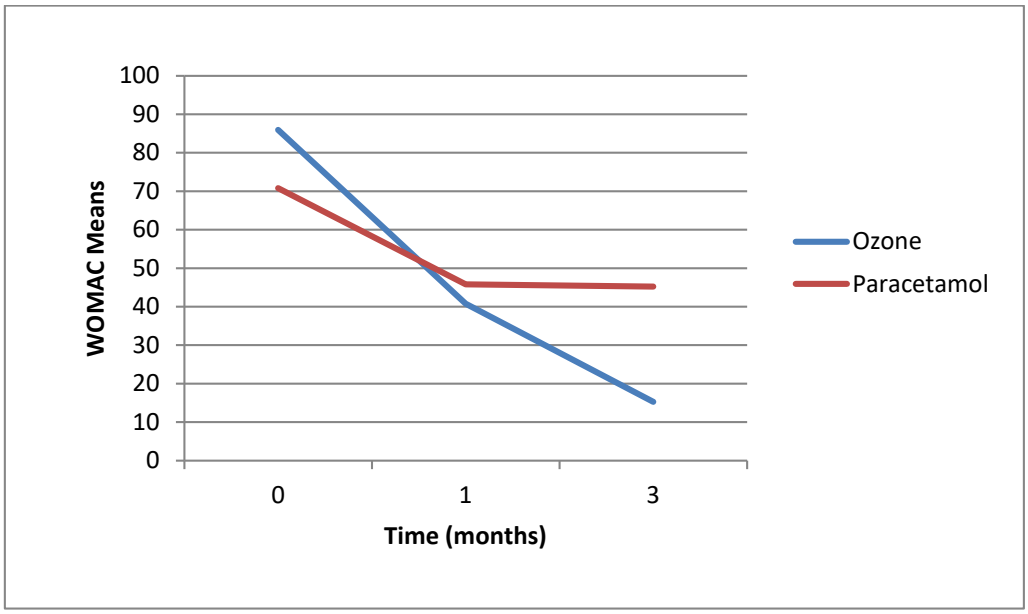

Figure 2: A graph plot of the mean WOMAC scores from baseline to 3rd month of follow up

The effect size of change in function as measured by WOMAC scores over time between the two groups was 0.252 and was found to be statistically significant (p=0.001) [Table 4].

V. DISCUSSION

This study showed that age is an important factor for occurrence of osteoarthritis of knee. The mean age of patients was 62.11±5.48 years, which is similar to a study done by Iqbal MN et al.[10] The increase in OA with age is likely a consequence of biologic alterations that occur with the aging process. These include decreased strength, decline in proprioception, a decreased response of chondrocytes by growth factors, and age-related accumulation of glycation end products, which is a haphazard process impairing the function of cartilage.[11] Majority of the patients were females constituting 22(62.9 %) of total study population which suggests that osteoarthritis is more prevalent in female population as supported by many literatures. Among the study population, housewives (45.7%) were mainly affected followed by teachers (25.7%).This findings correlates with a study done by Felson DT[12] in which he found that occupations characterized by repetitive joint loading and knee bending increases the risk of developing osteoarthritis.

The findings in improvement of pain with ozone therapy corresponds to the study done by Al-Jaziri et al.[13] Their study validated the analgesic effect of ozone injection on osteoarthritis of joints and spine. Another study by Bocci VA et al[14] also validated ozone having anti-inflammatory and analgesic effect. This study also showed functional improvement as measured by WOMAC Score in both the groups.

All patients completed the study. However, one patient developed swelling of the joint and three patients had increased in pain following ozone injection which subsided within 48 hours. No adverse reaction occurred in any patient in both the groups, which suggests that ozone therapy in osteoarthritis knee is safe, if not otherwise contraindicated. In a study done by Gheza et al[15] on ozone therapy, established that it is a simple technique with no complication for pain relief in knee pain particularly in early OA and soft tissue therapy inflammation.

Non-blinded study, small sample size and shorter follow up are the main limitations of the study.

VI. CONCLUSION

Single intra-articular ozone therapy is effective for pain relief and functional improvement in OA knee (Grade 2 and 3) in the first 3months after injection. However, larger sample size with a long term follow up will be necessary to see if the improvement is maintained.

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