

Efficacy of Intra-Articular Ozone Versus Hyaluronic Acid In Patients of Knee Osteoarthritis

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ABSTRACT

Objective: To determine the analgesic efficacy of ozone gas versus hyaluronic acid solution in knee osteoarthritis patients.

Study Design: Quasi-experimental study.

Place and duration of study: Department of Pain Medicine, Combined Military Hospital, Rawalpindi Pakistan, from Jun to Dec 2020.

Methodology: Seventy patients suffering from knee osteoarthritis fulfilling the inclusion criteria were included in this study and were randomly assigned to two equal groups to undergo intra-articular knee injection using either Hyaluronic Acid (Group-H) or Ozone (Group-O). Improvement in the numeric rating scale (NRS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale were recorded 1, 3 and 6 months after the procedure.

Results: In both groups, the pain score (Group-H Pre-procedure NRS =7.66±0.87 vs. Post-Procedure 6 month NRS =4.74±0.70, Group-O Pre-procedure NRS =7.86±0.88 vs. Post-Procedure 6 month NRS=4.46±0.92) and WOMAC (Group-H Pre-procedure =77.60±7.93 vs. Post-Procedure 6 month =40.31±6.81, Group-O Pre-procedure=75.54±9.40 vs. Post-Procedure 6 month =38.37±8.98) score improved. However, the NRS pain score (p -value=0.21) and patient WOMAC score (p -value=0.31) were not significantly different between groups.

Conclusion: Neither Hyaluronic Acid nor Ozone appears superior in decreasing pain scores or physical limitations, particularly for knee osteoarthritis.

Keywords: Hyaluronic acid, Osteoarthritis, Pain, Pain Measurement, Analgesia

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INTRODUCTION

Knee osteoarthritis (OA) is one of the most common types of degenerative conditions prevalent in the older population.¹ It is a clinical syndrome of joint disability having features of slow degeneration of joint cartilage, formation of osteophytes, remodelling of subchondral bone and joint inflammation.² Owing to associated pain and limited mobility, this disease may rightly be considered a source of widespread disability worldwide.³ When oral analgesics are ineffective, other therapies such as joint injections (corticosteroids, blood-derived products, viscosupplements and prolotherapy) are the last minimally invasive option that can be carried out without causing increased morbidity and mortality.⁴ Early intervention can help in the slowing of disease process.⁵ Many drugs have been studied that when deposited in the knee joint provides good pain relief with improved range of motion. Ozone is one of the less common drugs used for intra-articular injection.⁶ However, recently, ozone has gained much importance as it is relatively cheap

with minimal side effects. Sophisticated equipment is not needed to administer ozone.

A few studies done worldwide have compared the effects of Hyaluronic Acid and Ozone on knee arthritis, and both methods have shown promising results. Giombini *et al.* compared Hyaluronic Acid and ozone in patients of knee arthrosis found that Ozone and Hyaluronic Acid were effective alone and in combination for symptomatic relief.⁷ A meta-analysis published by Hedayatabad *et al.* also compared Hyaluronic Acid with ozone. The systemic review showed that there was no long-term difference between the two groups in terms of pain relief and WOMAC score.⁸ Another meta-analysis by Li *et al.* showed similar results. Improvement in WOMAC scores was similar in both groups.⁹ Yet another meta-analysis by Raeissadat *et al.* compared Ozone with the control group and concluded that ozone was beneficial for at least three to six months in cases of a mild form of knee osteoarthritis.¹⁰

Existing research has provided conflicting evidence regarding the superiority of either Hyaluronic Acid or Ozone in improving pain and functionality in patients with knee osteoarthritis. This

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study addresses this gap by conducting a rigorous investigation, utilizing the Numeric Rating Scale (NRS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale as outcome measures.

METHODOLOGY

The quasi-experimental study was conducted in the Department of Pain Medicine, CMH Rawalpindi, Pakistan from June to December 2020 after approval (ERB No: 172/6/21). WHO sample size calculator was used to estimate the sample size from an already published study taking the fall in WOMAC score after intervention from 20.4 ± 5.0 to 17.1 ± 4.2 .¹¹ A non-probability consecutive sampling technique was used to gather the required sample.

Inclusion Criteria: Patients aged 40 to 75 years, with knee osteoarthritis, Grades 2 to 4 on radiography using the Kellgren–Lawrance radiologic scoring (KLS) system; symptom duration of at least six months not relieved by oral medications were included.

Exclusion Criteria: Patients with recent trauma or lower limb fracture; post-knee surgery; recent intra-articular injection (past six months); limb deformity; coagulopathy; cancer metastasis; pregnancy; septic arthritis; glucose 6-phosphate dehydrogenase deficiency, were excluded.

Patients were equally divided into two groups using a lottery method for randomization: Group-H and Group-O. Group-H: 2ml (20mg) Hyaluronic acid (Injection Hyalgan®, Italy) was injected. Group-O: 10 ml (33 µg/mL) Oxygen-ozone gas (O₃, Elite promolife ozone generator) was injected (Figure).¹²

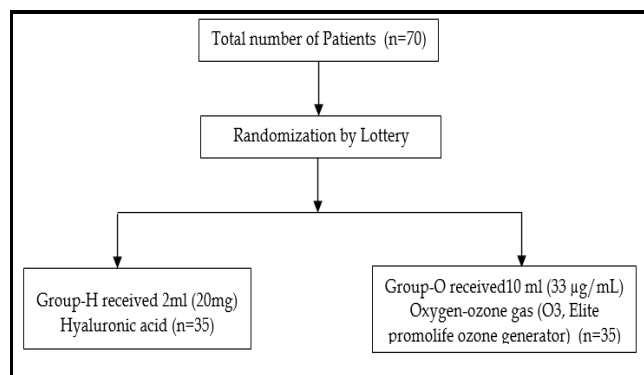


Figure: Patient Flow Diagram (n=70)

All procedures were performed under fluoroscopic guidance under strict aseptic conditions. A. A 22G spinal needle was inserted using the classic anteromedial approach with the affected knee in a

flexed position after a topical anaesthetic ethyl chloride spray. The needle tip's location in the joint space was confirmed by injecting a dye solution. After confirmation of the needle tip, Oxygen-ozone gas or Hyalgan solution was administered.

Three consecutive weekly injections were carried out. A pain medicine consultant and a pain medicine trainee performed all procedures. All patients were instructed to avoid activity for 48 hours. If they experienced post-procedure pain, they should apply an ice pack if needed. Patients were also advised to continue knee strengthening exercises and lifestyle modification.

Patients were evaluated before treatment and then after completion of treatment protocol. Post-procedure evaluation was done at one month, three months and six months. Primary outcome: Pain score was assessed using a numeric rating scale (NRS). It is a scale from 0 to 10, where 0 means no pain and 10 signifies the worst possible pain. The secondary outcome, improvement in function, was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale, which has three domains: pain, stiffness and a patient's physical functioning. The questionnaire was explained to the patient in whichever language they understood. The scores are then summed up for each parameter, giving a score range of 0-20 for pain, 0-8 for stiffness, and 0-68 for Physical Function.

Statistical Package for Social Sciences (SPSS) version 26.0 was used for the data analysis. Quantitative variables were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. The Shapiro-Wilk test was used as a test of normality. Mann-Whitney U test was used for non-parametric data, and an independent sample t-test was used for parametric data. The *p*-value of ≤0.05 was considered as significant.

RESULTS

In this study, 70 patients with knee osteoarthritis were included. The mean age in Group-H was 56.34 ± 9.37 years, and 56.89 ± 9.43 years in Group-O (Table-I).

Before treatment, there was no significant difference in mean NRS between both groups (Group-H: 7.66 ± 0.87 versus Group -O: 7.86 ± 0.88) and WOMAC score (Group-H: 77.60 ± 7.93 versus Group-O: 75.54 ± 9.40). After the intervention, there was no statistically significant decrease in either NRS or WOMAC score at one, three, and six months (Tables-II & III). NRS in

Group-H decreased to 3.49±0.74 and 3.63±0.81 in Group-O after one month ($p=0.72$). After three months, it decreased to 3.69±0.93 in Group-H and 3.31±0.68 in Group-O ($p=0.08$), and at six months, it was 4.74±0.70 and 4.46±0.92 in Group-H and Group-O, respectively ($p=0.21$)

Table-I: Demographic Data of the Patients (n=70)

| Parameters | Group-H (n=35) | Group-O (n=35) |
|--|----------------|----------------|
| Age (years): | | |
| Mean±SD | 56.34±9.37 | 56.89±9.43 |
| Gender: n(%) | | |
| Male: | 13(37) | 15(43) |
| Female | 22(63) | 20(57) |
| Body Mass Index (kg/m²): | | |
| Mean±SD | 31.70±3.69 | 31.56±3.66 |
| Grade of osteoarthritis: n (%) | | |
| II | 10(29) | 9(26) |
| III | 17(49) | 14(40) |
| IV | 8(22) | 12(34) |

Table-II: Comparison of Numeric Rating Scale Score over Time (n=70)

| | Group Hyaluronic Acid | Group Ozone | p-value |
|-------------|-----------------------|-------------|---------|
| Baseline | 77.60±7.93 | 75.54±9.40 | 0.32 |
| At 1 month | 31.31±9.22 | 29.57±7.99 | 0.40 |
| At 3 months | 31.94±8.42 | 30.09±7.48 | 0.33 |
| At 6 months | 40.31±6.81 | 38.37±8.98 | 0.31 |

*NRS: numeric rating scale

WOMAC scores also decreased over time. In Group-H and Group-O, the WOMAC score was 31.31±9.22 and 29.57±7.99 a month after injection ($p=0.40$), 31.94±8.42 and 26.86±6.33 three months after injection ($p=0.33$), and 40.31±6.81 and 36.03±9.80 six months after injection ($p=0.31$). All the patients were followed for six months. No adverse event or complication was recorded during the study duration in any patient.

DISCUSSION

In our study, we compared intra-articular Hyaluronic Acid with an ozone-oxygen mixture. Our study concluded no significant difference between the two groups based on the NRS and WOMAC scale. The findings in our study are consistent with a few other studies. Raeissadat et al. studied one hundred and seventy-four patients. Total WOMAC score decreased from 40.8±9.8 to 20.4±4.9 ($p<0.01$) in the Ozone group and from 38.5±7.9 to 17.1±4.2 ($p<0.01$) in the Hyaluronic Acid Group in the first three months. They concluded that there was no difference in NRS and WOMAC scores between the two groups when regularly followed up for six months.¹¹ Another meta-

Table-III: Comparison of Western Ontario and McMaster Universities Arthritis Index (WOMAC) score over time (n=70)

| Variables | Group Hyaluronic Acid | Group Ozone | p-value |
|-------------------------|-----------------------|-------------|---------|
| | Median (IQR) | | |
| NRS Score Pre Procedure | 8(1) | 8(1) | 0.34 |
| NRS Score at 1 month | 4(1) | 3(1) | 0.44 |
| NRS Score at 3 months | 4(1) | 3(1) | 0.08 |
| NRS Score at 6 months | 5(1) | 4(1) | 0.21 |

analysis by Raeissadat *et al.* studied four hundred and twenty-eight patients in five randomized controlled trials. These studies compared control with ozone injections. The mean difference (MD) between the groups for NRS in the first month was -0.23 with a *P*-value of 0.71 (the negative value favoured ozone). In contrast, this difference in the third and sixth months reached 1.04 and 1.31, respectively, favouring the control group. The results showed that ozone was better than placebo in the initial three months, but later on, there was no difference between the groups.¹⁰

Similar results were seen in a few other studies, which showed no difference between ozone and Hyaluronic Acid groups.^{8,12} A few studies had different results than our study. Likewise, similar results were seen in a few other studies.⁹⁻¹⁵ Some studies compared ozone with platelet-rich plasma. In contrast, others compared it to intra-articular corticosteroid injection, especially in the elderly. All of them have been shown to decrease pain scores substantially and improve physical functioning.¹⁶⁻¹⁸

In our study, pain relief was comparable between the groups. NRS and WOMAC scores showed an improved trend up to the third month but no superior analgesic efficacy over another. Both drugs have an effect for up to six months, and the cycle can be repeated if required. We compared both injections on a weekly injection regimen. Both modalities appeared to be safe.

LIMITATIONS OF STUDY

A few limitations of this study included using low to moderate doses of Hyaluronic Acid and Ozone and fewer intervention sessions. In addition, the small sample size, single-centre and limited duration study, co-morbid medical conditions and non-random sampling technique may confound the results to some extent. We recommend conducting more studies on this subject using higher doses of both agents, frequent sessions, and potentially long-term follow-up.

CONCLUSION

Ozone is a safe and relatively cheaper alternative for treating knee osteoarthritis-related functional limitations. Although no significant difference in analgesic efficacy was established between treatment groups, both modalities have demonstrated good effects on pain control and physical functioning for at least three months.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

1,2: Conception, study design, drafting the manuscript, approval of the final version to be published.

3,4: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

5,6: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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