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## The role of ozone and its potentiating effect on steroids and vesicosupplement injections for knee osteoarthritis

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### Abstract

One hundred five patients were included, their ages ranging from (25 to 80) years old suffering from chronic knee joint pain for more than 3 months due to mild, moderate, and advanced osteoarthritis. The cases were documented by detailed history-taking, clinical examination, x-ray findings, lab investigations, and ultrasound evaluation. The procedure comprised intra articular ozone (O<sub>3</sub>) therapy, ozone with steroid, or ozon with hyaluronic acid injection, for 105 patient. Aspiration of the effusion of an amount ranging from (15-75 ml) form 24 patients, volume and concentration of medical ozone was used(15-20 ml of 20-30 µg/ml), divided into five sessions by one week interval regularly using a lateral or medial suprapatellar approach under ultrasound guidance by a short axis view over the suprapatellar recess. The aim of this study is to assess the (Role of Ozone and Its potentiation effect on Steroids and Vesicosupplement) Injections in knee OA. The current study revealed that good responses regarding pain and joint function were commonly obtained in mild (85.7%) and moderate (81.5%) OA, followed by advanced OA (51.4%), respectively, in comparison to moderate or poor responses obtained in mild OA (14.3%), moderate OA (18.5%), and advanced OA (48.6%), respectively. Ozone is a promising interventional pain treatment for patients with knee OA if it is used in the form of weekly sessions and continuously for 5 sessions, regardless of the joint, and it is advisable to use O<sub>3</sub> routinely at the end of interventional pain procedures safely because of its properties.

**Keywords:** Ozone, Steroids, & vesicosupplement injections of OA knee, Injection of OA knee with Ozone, steroids, & vesicosupplement

### Introduction

One of the most prevalent kinds of degeneration of the knee joint and the most prevalent cause of disability is Knee osteoarthritis (OA) in the United States of America [1]. It is reported that more than 10 million Americans have knee OA, and it has been a serious social problem. Recently, the population's aging and obesity have contributed to the increasing incidence of OA of the knee. Pain, stiffness, and mobility limitations are the main symptoms. Reducing pain and improving joint mobility are the main targets of traditional treatment [2]. In the presence of many kinds of therapy, involving daily activity modification and analgesia infiltration in the periarticular region, the ideal therapy is still controversial [3-5]. One of the alternative therapies is intra-articular injection of hyaluronic acid (HA) products in knee OA, which is generally utilized [6]. Intra-articular injection of hyaluronic acid (HA) increases the endogenous synthesis of HA and causes an enzymatic (chondro-degenerative enzyme) inhibition that leads to an inflammatory reaction. A study carried out by Altman *et al.* showed that HA injections in knee OA patients are commonly fully tolerated, supply continuous pain relief, and lead to patient function improvement [7]. One of the modalities for therapy in painful situations like lumbar disc herniation and degenerative joint disease is a mixture of oxygen and ozone called oxygen-ozone [8]. The positive new studies of clinical trials have revealed the positive function of oxygen-ozone injection in the therapy of knee OA [9]. There is still a mystery surrounding the safety and efficacy of oxygen-ozone intra-articular injection in comparison to treatment with intra-articular HA because of limitations in the published article and a mainly small sample size.

### Patients and Methods

This is a case series study that included 105 patients from a private clinic ages (25-80) suffering from chronic knee joint pain for more than 3 months due to mild, moderate, or advanced (who are not candidates for knee replacement or have refused surgery) osteoarthritis.

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The cases were documented by detailed history-taking, clinical examination, x-ray findings, lab investigation, and ultrasound evaluation. The procedure comprised the procedure comprised intraarticular ozone (O<sub>3</sub>) therapy, ozone with steroid, or ozon with hyaluronic acid injection, for 105 patient. Aspiration from 24 patients of an amount ranging from 15 to 75 ml, the volume and concentration was used of medical injection of ozone (15-20 ml of 20-30 µg/ml) divided into five sessions every week regularly using a lateral or sometimes medial suprapatellar approach under ultrasound guidance by a short axis view over the

suprapatellar recess (pouch or bursa). This approach was selected because it is safer, carries less risk for articular cartilage injury, causes less soreness after injection, has a lower chance of infection, and even if there is a small amount of fluid, guides us to a successful intraarticular injection.

**Follow up of the patient**

All patients were followed up every 2 weeks, at the 6-month interval, and then for 1-2 years. The distribution of the patients was as follows:

**Table 1:** Mild OA (14) patients

Sessions of O <sub>3</sub>	Details of the procedures
1 <sup>st</sup> (5 patients)	4 patients unilateral (Lt or Rt), 1 patient bilateral knee joints.
2 <sup>nd</sup> (5 patients)	4 patients unilateral (Lt or Rt), 1 patient bilateral knee joints and 1 patient from them underwent for aspiration
3 <sup>rd</sup> (2 patients)	2 patients; 1 patient unilateral+ Hyaluronic Acid (HA), 1 patient for bilateral knee joints.
4 <sup>th</sup> (1 patient)	One patient unilateral.
5 <sup>th</sup> (1 patient)	Patient for bilateral knee joints+20mg Triamcinolone in each.

**Table 2:** Moderate OA (54) patients:

Sessions of O <sub>3</sub>	Details of the procedures
1st (17 patients)	15 patients unilateral (Lt or Rt) and 2 patient bilateral knee joints; 7 of them underwent aspiration and 6 patients received intra articular steroid (1pt 20 mg methylprednisolone, 5 patients 20 mg triamcinolone and 1 patient 8mg dexamethasone) and 6 patients received Hyaluronic Acid(HA).
2nd (15 patients)	15 patients unilateral (Lt or Rt);2 patients from them underwent aspiration and 5 patients received intra articular steroid(1 patient 20mg methylprednisolone, 3 patients 20mg triamcinolone and 1 patient 8mg dexamethasone) and 4 patients received Hyaluronic Acid (HA).
3rd (14 patients)	11 patients unilateral, 3 patient for bilateral knee joints; 2 patients received intra articular steroid (1 patient 4mg dexamethasone and 1 patient 4mg betamethasone), 4 patients received Hyaluronic Acid(HA).
4th (5 patients)	4 patient unilateral and 1 patients bilateral knee joints; 1 patient received Hyaluronic Acid(HA)
5th(3 patients)	2 patients unilateral, 1 patient for bilateral knee joints; 2 patients received Hyaluronic Acid (HA) bilaterally, 1 patient unilateral.

**Table 3:** Advance OA 37 patients:

Sessions of O <sub>3</sub>	Details of the procedures
1 <sup>st</sup> (14 patients)	12 patients unilateral (Lt or Rt), 2 patient bilateral knee joints; 4 patients from them underwent aspiration(one of them bilateral) 2 patients received HA,
2 <sup>nd</sup> (10 patients)	6 patients unilateral (Lt or Rt), 4 patients bilateral knee joints & one of them underwent aspiration, 5 patients received HA (one of them bilateral), 1 patient received 8mg dexamethasone.
3 <sup>rd</sup> (8 patients)	5 patient unilateral, 3 patient for bilateral knee joints, one of them underwent aspiration bilaterally, 3 patients received HA and one patient of them received bilaterally 20mg Triamcinolone for each joint
4th (2 patients)	1 patient unilateral and 1 patient bilaterally
5 <sup>th</sup> (3 patients)	2 patients for unilateral and 1 patient bilaterally; one patient underwent bilateral aspiration of knee joints+20mg Triamcinolone in each joint.

Vesicosupplement hyaluronic acid-HA (arthromac 90mg/ml 3ml 3%)



**Fig 1:** sterilization of entry point



**Fig 2:** needle inside the suprapatellar recess



**Fig 3:** medical ozone (O<sub>3</sub>) injection



**Fig 4:** Vesicosupplement (arthromac) injection



**Fig 5:** Steroid injection



**Results**

The current study revealed that disease severity was as follows: 83 (79.05%) of the sample were females in comparison to 22 (20.95%) male patients, as shown in Table 4.

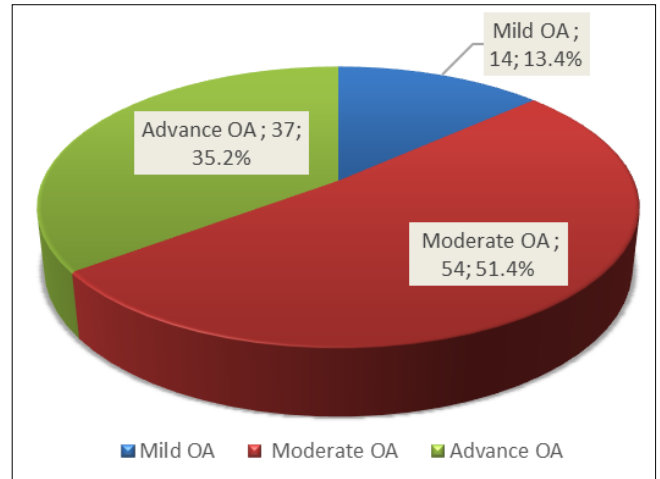
**Table 4:** The sex of the study cases

	Frequency	Percent
Male	22	20.95
Female	83	79.05
Total	105	100.00

The current study revealed that disease severity was as follows: moderate 54 (51.4%), advanced OA 37 (35.2%), and the least mild OA 14 (13.4%), as in table 5 and figure 1.

**Table 5:** The study cases arranged according to the severity of the disease

	Frequency	Percent
Mild OA	14	13.4
Moderate OA	54	51.4
Advance OA	37	35.2
Total	105	100.0



**Fig 1:** The distribution of the study sample according to disease severity

The current study revealed that mild, moderate and massive effusion present in 24 (22.8%), and the remaining without joint effusion 81 (77.2%) as in sixth table.

**Table 6:** The study cases arranged regarding the joint effusion

	Frequency	%
joint effusion mild, moderate and massive effusion	24	22.8
without joint effusion	81	77.2
Total	105	100.00

The current study revealed that the sites of effusion were as follows: left knee 13 (54.2%), right knee 8 (33.3%), both

knees (12.5%), as in Table 7.

**Table 7:** The distribution of patients with effusion according to site of effusion

Effusion site	Frequency	Percent
Rt Knee	8	33.3
LT Knee	13	54.2
Both	3	12.5
Total	24	100.0

The current study revealed that good responses were commonly obtained in mild (85.7%) and moderate (81.5%) OA, followed by advanced OA (51.4%), respectively, in

comparison to moderate or poor responses in mild OA (14.3%), moderate OA (18.5%), and advanced OA (48.6%), as shown in the eighth table.

**Table 8:** The study cases arranged regarding the response to treatment intervention

Response to Ozone therapy	Mild OA		Moderate OA		Advanced OA	
	Frequency	%	Frequency	%	Frequency	%
Good response	12	85.7	44	81.5	19	51.4
Moderate or poor response	2	14.3	10	18.5	18	48.6
Total	14	100.0	54	100.0	37	100.0

$X^2= 11.83$ ,  $df= 2$ ,  $P$  value =0.003 significant

Those with mild OA changes 5(35.7%), had relief of symptoms for 6-12 months, and 7(50%) for > 12 months, in comparison to moderate OA changes 16(29.6%), 26(48.1%)

respectively, and sever OA changes 22(59.5%), and 10(27%) respectively.as shown in table 9.

**Table 9:** The study cases arranged regarding the time of relief after treatment intervention

Time of relief	Mild OA		Moderate OA		Sever OA	
	Frequency	%	Frequency	%	Frequency	%
< 6 month	2	14.3	12	22.3	5	13.5
6-12 month	5	35.7	16	29.6	22	59.5
> 12 months	7	50.0	26	48.1	10	27.0
Total	14	100.0	54	100.0	37	100.0

$X^2= 8.6$ ,  $df= 4$ ,  $P$  value =0.07 not significant

Patients treated with Ozone therapy alone had relief time of > 12 months in 28(63.3%) patients, in comparison to those treated with Ozone and HA 15(40.5%) patients, and those treated with Ozone and steroids 7(29.2%), as shown in table 10.

**Table 10:** The distribution of the study sample according to type of intervention and time of symptoms relief.

Time of relief	ozone		Ozone + HA		Ozone+ Steroid	
	Frequency	%	Frequency	%	Frequency	%
< 6 month	7	15.9	9	24.4	6	25.0
6-12 month	9	20.5	13	35.1	11	45.8
> 12 months	28	63.6	15	40.5	7	29.2
Total	44	100.0	37	100.0	24	100.0

$\chi^2=8.8$ ,  $df=4$ ,  $P$  value =0.06 not significant

## Discussion

K.D. Allen in 2022 revealed that knee OA is an increasingly common illness with global effects on numerous health indicators [10]. Our current study revealed that disease severity was as follows: 83 (79.05%) of the sample were females, compared to 22 (20.95%) male patients. Knee OA happens more prevalently in the age group of women older than 45 years, and it is more prevalent in men before 45 years of age. There were published studies on women determining the association between estrogen and OA incidence in women with menopausal years that revealed paradoxical outcomes [11-15]. This agreement with Kapstad H in 2008 revealed that the great portion of the sample was women, with a mean age of 69.1 years for the knee (78%). The current study revealed that disease severity was as follows: moderate 54 (51.4%), advanced OA 37 (35.2%), and the least mild OA 14 (13.3%). The same researcher used cut-point calculations used in the classification of OA of the knee to determine that mild pain was present in 22% of the sample, moderate pain was present in 43%, and severe pain was present in 35% of the sample [16].

This also agrees with Pal CP in 2016 found that the general incidence of OA in the knee joint was shown to be 28.7%. The related factors were shown to be women, obesity, age, and sedentary work. Pal CP in 2016 found that the relationship between sex and knee OA was in accordance with the written studies on knee OA. Knee OA was shown to be more common in women (31.6%) than in men (28.1%) [17]. Our current article revealed that good responses were commonly obtained in mild and moderate OA, followed by advanced OA. Our research found that most of the patients from the first session of ozone injection seemed to have a noticeable improvement regarding pain and joint function and also revealed that ozone with steroids prevents the re-aggregation of fluids in the joint after withdrawing it and increases the effectiveness and duration (short-term relief 2 weeks to 2 months) of the steroids to up to 1 year, noting that the dose that we used for the steroids is 20 mg Kenacort (Triamcinolone), 20 mg methylprednisolone (Depomedrol), (Dexamethasone 4-8 mg), and (Betacortacort 4mg), which are small doses for the knee joint.

This agrees with Fernández-Cuadros *et al.*'s 2022 finding that Ozone is a valid option for the management of knee osteoarthritis in a real-world rehabilitation setting because of its anti-inflammatory, metabolic, and anabolic properties. Ozone tends to downregulate the pro-inflammatory IL-6 cytokine. Ozone has a metabolic or hypoglycemic effect on obese or diabetic knee osteoarthritis patients by reducing

IGF-1. Ozone has an anabolic effect on non-diabetic and non-obese patients by improving IGF-1. Ozone reduces other biomarkers of inflammation (CRP, ESR, and uric acid) and improves pain, function, and quality of life [18]. This also agrees with Korkmaz MD *et al.*, who in 2022 found that both ozone and HA injections were effective treatment methods for KOA [19].

I also agree with some studies (Bocci V in 1998) that identified an evident post-injection fall in the amount of cytokines in charge of inflammation and progression of OA of the knee [20]. In a study carried out in India by Mishra SK in 2011, the study team carried out a cross-over study with two treatment types in a group of 46 patients with OA of the knee joint: mono methylprednisolone injection in comparison to ozone injections at three monthly intervals. Six months later, the study team found that the response rate was 80% in the ozone group in comparison to 60% in the steroid group [21]. Further articles (Hashemi M. in 2015 and ACR 2015 Annual Meeting) revealed that intra-articular injection of ozone had useful effects similar to those of hypertonic dextrose and was greatly efficacious in comparison to only air injection in knee OA symptoms management [22, 23].

The current study revealed that ozone injection with hyaluronic acid increases its effectiveness to improve pain and joint function and the desired period (usually 6 months) of it, which may reach >1 year for advanced OA patients or > 2 to 3 years for mild and moderate OA patients, even up to 4 years in mild OA cases. The more ozone sessions are 3 or more, the percentage and duration of benefit will be higher and longer, and the patients get benefits as follows: 12 from 14 of mild OA patients, 44 from 54 of moderate OA patients and 19 from 37 of advanced OA patients. The current study did not record any pain after the injection for any patient, nor any infection of the joint. This agrees with Momen Zadeh S's 2014 study, which compared ozone and HA efficacy in two groups of 30 participants with knee OA. At the end, they revealed a powerful amelioration in two groups in comparison to baseline; however, significant differences between the two kinds of therapy were absent through a short-term follow-up. Type. This means that the combination of ozone and HA acts in synergy [24].

Lopes de Jesus *et al.* found that ozone was more effective than placebo in pain reduction after 8 weeks of treatment. Similarly, we found that the combination of both HA and ozone injections works in synergy because they potentiate the decrement of pain intensity and improve joint function [25].

In the whole past literature that had carried out a comparison between injections of HA intra-articular and ozone, both kinds of therapy had been confirmed to be efficacious in the treatment of pain and other symptoms; however, there was a persistent debate concerning the outcome concerning the period of pain-free duration and impact size of each modality. This agrees with Aliyev D. *et al.*'s 2023 finding that the intra-articular injection of ozone, applied once a week for 4 weeks, resulted in a reduction in pain in stage 2-3 knee OA without any side effects [26].

An extra identical article done by Giombini in 2016 on three groups of patients with HA, ozone, and combination therapy revealed a greater amelioration with the combination therapy in terms of clinical scores in comparison to the remaining two modalities of therapy in a program of follow-up for a 2-month period [27]. This agrees with Babaei-Ghazani A's 2018 finding that in the group treated with

oxygen and ozone, there was a great and significant decrease in the joint effusion. The two modalities of treatment consisting of oxygen-ozone injections and steroids are efficacious in OA knee patients. It also revealed that the efficacy of oxygen-ozone injections persisted for longer periods in comparison to those with injections of steroids into the knee joint [28].

This also agrees with Antonio Oliviero *et al.*'s 2019 finding that ozone, acting on various inflammatory pathways, could be a promising therapeutic weapon capable of reducing pain while at the same time promoting the reacquisition of function and quality of life. It was also found that the most promising protocol for reducing pain is an intra-articular injection of 20 µg/mL of O<sub>3</sub>, once a week for four consecutive weeks. It has also been shown that ozone can be used as a safe, effective, conservative therapeutic option with contained costs in the short-term management of knee OA [29].

Mustafa Yassin *et al.* in 2022 found that in all criteria, including pain relief, functionality, and quality of life, the efficacy of ozone was confirmed. [30] So, in agreement with the present research, although there was a great amelioration in both groups of patients, there were non-significant differences in terms of the safety and efficacy of both treatment modalities [21, 25].

### Conclusions

Therefore, ozone is a promising interventional pain treatment for OA knee joint patients if it is used in the form of weekly sessions (every seven days) and continuously for five sessions. Ozone also gives potentiation effect for steroid and hyaluronic acid injections.

Also, with regardless to the joint, it is advisable to use O<sub>3</sub> routinely at the end of interventional pain procedures safely because of its properties.

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