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Effect of intraarticular ozone, prolotherapy or dexmedetomidine in pain limitation in knee osteoarthritis: A randomized prospective study

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Abstract
Background: Osteoarthritis (OA) is a heterogenic group of different etiology disorders with similar morphological, biological, and clinical outcomes and manifestations. We aimed to compare the intraarticular ozone injection, prolotherapy or dexmedetomidine effectiveness in knee OA (KOA) patients.
Methods: This randomized prospective study was carried out on 60 cases aged from 30 to 65 years old, both sexes, diagnosed with stage 1-3 osteoarthritis according to the Kellgren-Lawrence Classification System (K-L). Cases were randomly allocated using computer generated randomization tables. into three equal groups: Group O received intra-articular (IA) ozone injection, group P received IA dextrose prolotherapy injection, group D received IA dexmedetomidine injection.
Results: A significant difference was indicated between the three groups with marked decrease of numerical rating scales, Western Ontario Mac Master OA Index, tumor necrosis factor (TNFα), analgesic requirement markedly decreased in Group O, group P more than group D (P<0.001, <0.001, 0.013, respectively). There was statistically significant difference between the three groups regarding AROM, extension, K-L (P=0.039, 0.019, 0.001, respectively) as knee flexion enhanced in group O and group P than group D.
Conclusions: We compared the IA ozone injection, prolotherapy or dexmedetomidine effectiveness in KOA patients. Analges in each group and according to TNF-α. Ozon and prolotherapy may yield satisfactory results more than dexmedetomidine in KOA.

Keywords: Intraarticular ozone, prolotherapy, dexmedetomidine, knee osteoarthritis

Introduction
Osteoarthritis (OA) is a heterogeneous group of disorders with varying etiologies, but which share similar biological, morphological, and clinical manifestations and outcomes. OA is now recognized as a disease that affects the entire joint, encompassing variations in the subchondral bone, articular cartilage, ligaments, synovial membrane, capsule, and periarticular muscles. The knee is the most frequently affected joint, and its OA has a significant impact on the medical, social, and economic sectors [1]. Older adults are significantly more likely to develop knee osteoarthritis (KOA). Treatments consist of medications (typically oral or topical NSAIDs, the latter of which frequently contains a proton-pump inhibitor), exercise, weight management, and training in self-efficacy and pain-coping skills [2]. In order to alleviate knee joint pain, intraarticular injections have been suggested [3]. Ozone therapy has been employed for an extended period in the OA treatment. Additionally, it has been demonstrated that it does not result in a substantial inflammation process or cartilage degradation. The positive ozone therapy effects are attributed to the production of reactive oxygen species and lipid oxidative products in the synovial fluid following injection. The anti-inflammatory effect is achieved through a variety of mechanisms, involving the inhibition of the release of proteolytic enzymes and the stimulation of the soluble receptor interleukin (IL-1) or other soluble receptors liberation and antagonists that are capable of blocking proinflammatory cytokines for example, interleukin (IL15, IL12, IL8, IL1) and tumor necrosis factor (TNF-α) [4].

Despite the fact that the precise ozone intra-articular (IA) injection remains unclear biochemical mechanism, there is a evidence growing body that supports the efficacy of ozone in the treatment of KOA. Ozone can suppress acute reactive mediators by downregulating TNF-α and TNF-R2 [5].

Prolotherapy is a procedure that involves the injection of a natural irritant into the soft tissue of an injured joint. Prolotherapy's mechanism of action remains incompletely comprehended. Nevertheless, the prevailing theory is that the injected proliferant replicates the body's natural healing process by triggering a local inflammatory cascade. This cascade triggers the growth factors release, collagen deposition, and the proliferation of chondrocytes, osteocytes, and fibroblasts, thereby strengthening injured or other joint-support structures or weakened ligaments that are the chronic pain source [6].

A selective α2-adrenergic agonist, dexmedetomidine exhibits significant analgesic and sedative effects. While its IA analgesic action mechanism is not yet fully understood, it is comparable to clonidine. Clonidine inhibits the norepinephrine release in peripheral afferent receptors by acting on presynaptic receptors. It also shows local anesthetic effects by inhibiting stimuli conduction through C and A-delta fibers [7]. Furthermore, when administered alone or in conjunction with bupivacaine, clonidine reduces pain behavior in animal experiments and enhances postoperative analgesia when administered via the IA route [8].

To the best of our knowledge, the OA progression has been linked to TNFα; however, the mechanisms by which TNFα simulates the OA progression and the signaling pathways it influences remain unknown [9].

We aimed to compare the intraarticular ozone injection, prolotherapy or dexmedetomidine effectiveness in KOA patients.

Cases and Methods

This randomized prospective study was performed on 60 cases aged from 30 to 65 years old, both sexes, diagnosed with stage 1-3 OA according to the Kellgren-Lawrence Classification System (K-L).

The patient provided written consent that was informed. The study was conducted from October 2022 to October 2023 after receiving approval from the Ethical Committee of Tanta University Hospitals.

Exclusion criteria were knee trauma history within the past month, severe cardiovascular disease, morbid obese cases (body mass index (BMI) of >35 kg/m2), rheumatiod OA disease, pregnancy, any surgical intervention of the knee, local infection at the site of injection, and bleeding diathesis.

Grouping and randomization

Randomization was done by computer-generated system. After obtaining the patient's consent, the list was concealed in sealed envelopes that were numbered and opened sequentially. Cases were randomly allocated utilizing computer generated randomization tables. into three equal groups: Group O received IA ozone injection, group P received IA dextrose prolotherapy injection, group D received IA dexmedetomidine injection.

All cases were subjected to: Analgesic consumption throughout the time of injection was calculated, age, gender, and BMI of the cases recorded, cases numerical rating scales (NRS) assessed at pretreatment baseline (BL), after 4th injection and after 3 months, cases Joint active Range of Motion (ROM) indicated with goniometry at the same periods. Normal active knee ROM (is Knee Flexion ROM: 135o i.e. fully bent, and Knee Extension ROM: 0o i.e. fully straight, to evaluate functional status, the Western Ontario Mac Master OA Index (WOMAC-OI) questionnaire completed by cases at the same periods, K-L, and measurement of TNF alpha.

The WOMAC-OI

Pain, stiffness, and OA-related dysfunction were to be assessed using a self-administered and disease-specific form. The individual required only approximately five minutes to respond to the items on the WOMAC scale. The Likert type of the WOMAC Persian version was employed in this paper. The Persian version is a dependable and uncomplicated procedure that provides five responses: extreme (4), severe (3), moderate (2), mild (1), and none (0). The patients' stiffness, pain, and functional restriction are all represented by the higher scores.

K-L [10]: which categorize knee OA into four stages based on radiological findings: Grade 4 (severe): Marked joint space narrowing, large osteophytes, severe sclerosis, and definite deformity of bone ends. Grade 3 (moderate): Moderate multiple osteophytes, some sclerosis, definite joint space narrowing, and potential deformity of bone ends. Grade 2 (minimal): Definite osteophytes and potential joint space narrowing. Grade 1 (doubtful): Possible osteophytic lipping and doubtful joint space narrowing.

Analgesics dose required for pain control before and after injections: One week before injections all cases were given etoricoxib 90 mg orally once daily and if pain was not controlled on this dose etoricoxib dose increased. Measurement of TNF alpha before and after the fourth injection. Blood samples were taken from each patient in each group to measure TNF before injection, after the 4th injection and after 3 months using ELISA kits.

All injections were done by physician who did not participate in data collection or analysis. Rescue analgesia was etoricoxib 90 mg/once daily week before the injection then we started our injection.

Intraarticular Ozone Method

For four sessions of IA knee ozone therapy using the lateral approach technique, cases were subjected to two sessions per week. this approach involves after sterilization of the whole knee skin with antiseptic solution insertion of a A22-gauge needle 1 cm above and 1 cm lateral to the superior patella lateral aspect at a 45-degree angle under completely aseptic condition, cases took 10 ml of 10 mcg/ml ozone as intraarticular injections.

Dextrose Prolotherapy Method

It’s solutions for maximum safety usually consist of sodium bicarbonate, dextrose, and a lidocaine, cases had two sessions a week for a total of four IA knee prolotherapy sessions. Dextrose prolotherapy solutions was injected into the knee joint (10 ml) by the lateral approach technique.

Dexmedetomidine Method

The IA dexmedetomidine group received injection of 10 ml dexmedetomidine 100 µg (1 ml) and (9ml) of isotonic saline. Cases had two sessions a week for a total of four IA knee dexametomidine injection sessions by lateral approach technique.

The primary outcome was decrease of Analgesic requirement for pain control after injection. The secondary outcomes were improvement of lifestyle according to WOMAC-OI evaluation, and improvement of knee joint cartilage regeneration by Kellgren-Lawren Classification System (K-L).

Sample Size Calculation

The sample size is calculated for each studied group based on the subsequent criteria: 95% confidence limit, 80% study power, group ratio 1:1:1, the range of expected primary outcome (efficacy) is 50-90%, and 5 cases will be added to overcome drop-out. Therefore, 20 cases will be recruited in each group.

Statistical analysis

SPSS v28 (IBM©, Armonk, NY, USA) was employed to conduct the statistical analysis. The normal data distribution was evaluated utilizing the Shapiro-Wilks test and histograms. ANOVA (F) test with post hoc test (Tukey) was utilized to analyse quantitative parametric data, which were presented as mean and standard deviation (SD). To compare each group, quantitative non-parametric data were presented as median and interquartile range (IQR) and analysed utilizing the Kruskal-Wallis test and Mann-Whitney-U test. The Chi-square test was expressed to analyse qualitative variables, which were presented as frequency and (%). Statistical significance was detected as P value < 0.05.

Results

Out of the 98 cases who were evaluated for eligibility in this study, 22 did not meet the criteria, and 16 regected to participate. The balance of 60 cases were randomly assigned to three groups, with 20 cases in each group. All cases who were allocated were statistically analysed and followed up. Figure 1.

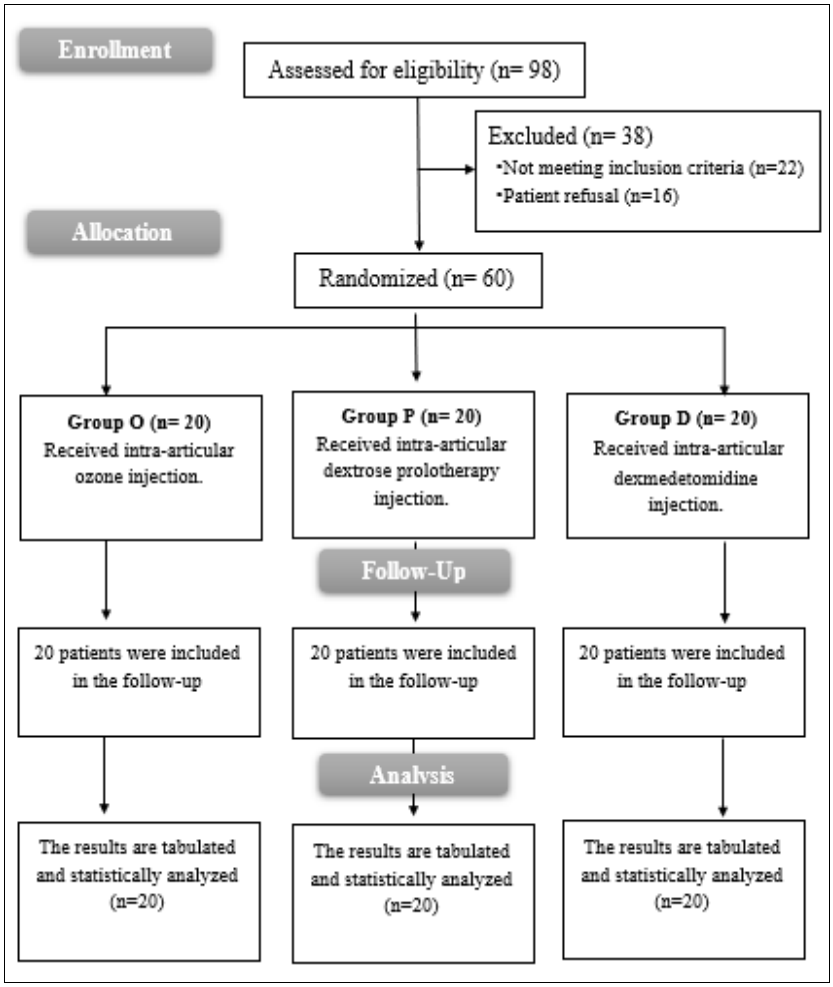

Fig 1: CONSORT flowchart of the studied patients

Table 1 shows no statistically significant difference between groups regarding to age, gender, and BMI.

Table 1: Comparison between the three studied groups according to demographic data

		Group O n=	Group P	Group D	P value
Age (years)	Mean ± SD	44.75 ± 9.73	50.95 ± 9.47	7.75 ± 45.0	0.098
	Median (IQR)	40.50 (36.5–52)	53.50 (44 – 59.5)	45.0 (42 – 54)	
Gender	Male	8 (40.0%)	7 (35.0%)	7 (35.0%)	0.931
	Female	12 (60.0%)	13 (65.0%)	13 (65.0%)	
BMI (kg/m^2)	Mean ± SD	33.92 ± 1.17	34.16 ± 0.80	34.17 ± 0.87	0.796
	Median (IQR)	34.0 (33.3 –34.8)	34.0 (33.6–34.9)	34.0 (33.8 –35)	

Data are presented as mean SD, median (IQR), number (%). IQR: interquartile range, BMI: body mass index.

A significant difference was indicated between the three groups with marked decrease of NRS, and WOMACs in Group O, group P more than group D (P<0.001). There was no statistically significant difference between the three studied groups according to Baseline pretreatment NRS, and WOMAC. Table 2.

Table 2: Comparison between the three studied groups according to NRS, and WOMAC

		Group O (n = 20)	Group P (n = 20)	Group D (n = 20)	P value
NRS					
Baseline pretreatment	Mean ± SD	7.75 ± 0.85	8.0 ± 0.97	8.05 ± 0.76	0.546
	Median (IQR)	8.0 (7.0 –8.0)	8.0 (7.0 –9.0)	8.0 (7.50 –9.0)	
After 4th injection	Mean ± SD	1.70 ± 0.73	2.10 ± 0.85	2.65 ± 0.67	0.002*
	Median (IQR)	2.0 (1.0 –2.0)	2.0 (1.0 –3.0)	3.0 (2.0 –3.0)	
Sig. bet. Grps		p_1=0.121, p_2<0.001*, p_3=0.044*			
After 3 months	Mean ± SD	1.40 ± 0.50	1.80 ± 0.70	2.65 ± 0.67	<0.001*
	Median (IQR)	1.0 (1.0 –2.0)	2.0 (1.0 –2.0)	3.0 (2.0 –3.0)	
Sig. bet. Grps		p_1=0.105, p_2<0.001*, p_3=0.001*			
WOMAC					
Baseline pretreatment	Mean ± SD	42.24 ± 4.68	42.16 ± 4.69	49.0±4.98	0.060
	Median (IQR)	43.0 (39.0 – 45.0)	42.0 (38.0 – 47.0)	42.16(38.0 – 47.0)	
After 4th injection	Mean ± SD	34.24 ± 4.70	39.24 ± 4.70	40.24 ± 4.70	**<0.001***
	Median (IQR)	34.0 (20.0 – 38.0)	39.0 (20.0 –42.0)	40.0(20.0-42.0)	
Sig. bet. Grps		p1=0.049*, p2<0.001*, p3=0.024*			
After 3 months	Mean ± SD	26.38 ± 3.39	26.38 ± 3.39	27.24 ± 4.70	<0.001*
	Median (IQR)	27.0 (24.0 – 29.0)	30.0 (24.0 – 29.0)	39.0(20.0-30.0)	
Sig. bet. Grps		p1=0.006*, p2<0.001*, p3=0.027*			

Data are presented as mean SD, median (IQR), number (%). IQR: interquartile range, NRS: Numerical rating scales, WOMAC: western ontario mac master osteoarthritis index, p1: p value for comparing between Group O and Group P, p2: p value for comparing between Group O and Group D, p3: p value for comparing between Group P and Group D, *: Statistically significant at $p \leq 0.05$.

There was a significant difference between the three groups regarding active ROM, and extension (P=0.039, 0.019, respectively) as knee flexion improved in group O and group P than group D. There was no statistically significant difference between the two groups according to Baseline pretreatment regarding AROM, and extension. **Table 3**

Table 3: Comparison between the three studied groups according to AROM, and extension

		Group O (n = 20)	Group P (n = 20)	Group D (n = 20)	P value
AROM					
Baseline pretreatment	Mean ± SD	111.6 ± 10.72	113.5 ± 9.71	109.3 ± 8.56	0.397
	Median (Min. – Max)	115.0 (90.0 –126.0)	117.0 (98.0 – 125.0)	108.0 (98.0 – 128.0)	
After 4th injection	Mean ± SD	133.4 ± 1.60	132.8 ± 1.94	131.5 ± 3.19	0.039*
	Median (Min. – Max)	134.0 (130.0 – 135.0)	133.0 (130.0 – 135.0)	132.0 (122.0 – 135.0)	
Sig. bet. Grps		p1=0.049*, p2<0.001*, p3=0.024*			
After 3 months	Mean ± SD	133.3 ± 1.80	132.8 ± 1.94	131.5 ± 3.19	0.057
	Median (Min. – Max)	134.0 (130.0 – 135.0)	133.0 (130.0 – 135.0)	132.0 (122.0 – 135.0)	
Extension					
Baseline pretreatment	Mean ± SD	17.85 ± 4.33	14.95 ± 5.03	15.30 ± 3.74	0.099
	Median (IQR)	18.0 (15.0 –20.50)	13.0 (11.0 –19.50)	14.0 (12.0 –18.0)	
After 4th injection	Mean ± SD	0.80 ± 1.36	1.50 ± 1.82	2.20 ± 1.58	0.019*
	Median (IQR)	0.0 (0.0 –2.0)	1.0 (0.0 –2.0)	2.0 (1.0 –4.0)	
Sig. bet. Grps		p_1=0.201, p_2=0.005*, p_3=0.126			
After 3 months	Mean ± SD	0.70 ± 1.34	1.50 ± 1.82	2.20 ± 1.58	<0.001*
	Median (IQR)	0.0 (0.0 –1.0)	1.0 (0.0 –2.0)	2.0 (1.0 –4.0)	
Sig. bet. grps		p_1=0.132, p_2=0.002*, p_3=0.128			

Data are presented as mean SD, median (IQR), number (%). IQR: interquartile range, AROM: active joint range of motion, p1: p value for comparing between Group O and Group P, p2: p value for comparing between Group O and Group D, p3: p value for comparing between Group P and Group D, *: Statistically significant at $p \leq 0.05$.

A significant difference was indicated between the three groups as TNFα, analgesic requirement markedly decreased in group O and group P than group D (P<0.001, 0.013). There was statistically significant difference between the three groups as K-L improved in group O and group P more than group D (P=0.001). There was no statistically significant difference between the three groups according to Baseline pretreatment regarding TNFα, analges, and K-L. Table 4

Table 4: Comparison between the three studied groups according to TNFα, analges, and K-L

		Group O (n = 20)	Group P (n = 20)	Group D (n = 20)	P value
TNFα					
Baseline pretreatment	Mean ± SD	138.6 ± 39.63	142.8 ± 31.38	148.5 ± 32.02	0.663
	Median (Min. – Max)	145.0 (65.0 – 196.0)	137.0 (83.90 – 187.0)	153.5 (93.80 – 193.0)	

After 4th injection	Mean ± SD	24.44 ± 0.27	24.54 ± 0.14	24.97 ± 1.04	0.024*
	Median (Min. – Max)	24.45 (24.0 – 24.90)	24.50 (24.30 – 24.80)	24.71 (24.06 – 29.0)	
Sig. bet. grps		p_1=0.869, p_2=0.027*, p_3=0.089			
After 3 months	Mean ± SD	23.40 ± 1.51	24.43 ± 0.21	24.87 ± 1.05	<0.001*
	Median (Min. – Max)	24.0 (20.0 – 24.90)	24.49 (24.0 – 24.80)	24.62 (24.0 – 29.0)	
Sig. bet. grps		p_1=0.009*, p_2<0.001*, p_3=0.388			
Analges					
Baseline pretreatment	Mean ± SD	109.5 ± 14.68	106.5 ± 15.31	112.5 ± 13.33	0.421
	Median (IQR)	120.0 (90.0 –120.0)	120.0 (90.0 –120.0)	120.0 (105.0 –120.0)	
After 4th injection	Mean ± SD	6.0 ± 12.31	12.0 ± 15.08	21.0 ± 17.14	0.013*
	Median (IQR)	0.0 (0.0 – 0.0)	0.0 (0.0 –30.0)	30.0 (0.0 – 30.0)	
Sig. bet. grps		p_1=0.214, p_2=0.003*, p_3=0.092			
After 3 months	Mean ± SD	0.0 ± 0.0	7.50 ± 13.33	18.0 ± 17.95	<0.001*
	Median (IQR)	0.0 (0.0 –0.0)	0.0 (0.0 –15.0)	30.0 (0.0 –30.0)	
Sig. bet. grps		p_1=0.082, p_2<0.001*, p_3=0.029*			
K-L					
Baseline pretreatment	Mean ± SD	2.60 ± 0.50	2.60 ± 0.50	2.65 ± 0.49	0.933
	Median (IQR)	3.0 (2.0 –3.0)	3.0 (2.0 –3.0)	3.0 (2.0 –3.0)	
After 4th injection	Mean ± SD	1.55 ± 0.51	1.55 ± 0.51	2.15 ± 0.49	0.001*
	Median (IQR)	2.0 (1.0 2.0)	2.0 (1.0 –2.0)	2.0 (2.0 –2.0)	
Sig. bet. grps		p_1=1.000, p_2=0.001*, p_3=0.001*			
After 3 months	Mean ± SD	1.60 ± 0.50	1.55 ± 0.51	2.15 ± 0.49	0.001*
	Median (IQR)	2.0 (1.0 –2.0)	2.0 (1.0 –2.0)	2.0 (2.0 –2.0)	
Sig. bet. grps		p_1=0.765, p_2=0.003*, p_3=0.001*			

Data are presented as mean SD, median (IQR), number (%). IQR: interquartile range, TNFα: tumor necrosis factor, K-L: Kellgren-Lawren Classification System, p1: p value for comparing between Group O and Group P, p2: p value for comparing between Group O and Group D, p3: p value for comparing between Group P and Group D, *: Statistically significant at $p \leq 0.05$.

Discussion

KOA is primarily caused by tear and wear due to aseptic articular cartilage inflammation, while OA is a degenerative joint disease distinguished by the slow progressive articular cartilage destruction [11]. Worldwide, approximately 250 million individuals are affected by KOA, as indicated by epidemiological surveys. The prevalence of KOA is on the rise as the general population ages, and it has emerged as a significant public health concern on a global scale [12]. KOA cases frequently experience limited mobility, knee pain, and, in severe cases, disability, all of which have a detrimental effect on their quality of life. [13].

In clinical practice, conservative therapy is the preferred option for cases and physicians due to its lower cost and postoperative sequelae or surgical complications absence. Compared to surgery, oral medications, and other treatments, IA drug injections could be essential for the OA management. [14]. Oral nonsteroidal anti-inflammatory drugs, chondroitin sulfate, and glucosamine have been demonstrated to be efficient for pain relief and functional enhancement in a short period as a conservative therapy form. However, there is currently no enhancement evidence in the underlying knee condition [15].

This study showed no significant difference between groups regarding to BMI, sex, and age. Regarding NRS pain score in group O, it was revealed that there is significant improvement in NRS after IA injection of knee with ozone as NRS mean (±SD) before injection was 7.75 ± 0.85 with significant improvement of NRS after the 4th injection of injection to become 1.70 ± 0.73, and minimally or no changes after 3 months with mean (±SD) 1.40 ± 0.50. However, in group P, it was revealed that there was significant improvement in NRS after inter articular injection of knee Prolotherapy as NRS mean (±SD) before injection was 7.0 ± 9.0 with significant improvement of NRS after the 4th injection to become 2.10 ± 0.85 but still less than the improvement in the first month of group O, and further improvement after 3 months with mean (±SD) 1.80 ± 0.70

But, in group D, it was revealed that there was significant improvement in NRS after inter articular injection of knee dexametomedine as NRS mean (±SD) before injection was 7.0 ± 9.0 with significant improvement of NRS after the 4th injection to become 2.65 ± 0.67 and less significant improvement after 3 months with mean (±SD) 2.65 ± 0.67.

The comparison between the studied groups showed that, there was no significant different between the two studied groups before injection but after 4th injection and 3 months follow up. A significant difference was indicated between the three groups (P<0.001) with marked NRS reduction in Group O, group P more than group D and also decrease analgesic requirements according to reduction in NRS.

In agreement with Farpour *et al*., [16] Of the 42 cases who were evaluated for inclusion in the study, 38 were ascribed to one of the two groups. In the end, the study was conducted on 34 patients, with the exception of 2 cases in each group who were excluded for personal reasons. The ozone + hypertonic saline group consisted of 15 cases (male=2, female=12), while the hypertonic saline group consisted of 19 cases (male=4, female=15). The VAS values decreased over time in each group independently ($p < 0.001$); although, no significant difference was assessed between the two groups ($p = 0.57$).

Also Gomes *et al*., [7] In an experimental rat KOA model induced with monosodium iodoacetate, the analgesic and anti-inflammatory dexmedetomidine effects administered via the i.a. route were evaluated at varying doses. The rats were divided into four groups, each of which contained 24 animals. The control group was not had OA induction; the OA, DEX-1 (dexmedetomidine in dose of 1μg/kg), and DEX-3 (dexmedetomidine in dose of 3μg/kg) groups were inducted with monosodium iodoacetate (MIA) via the i.a. route on the right knee. In comparison to the control group, the OA, DEX-1, and DEX-3 groups demonstrated significant decreases in pain thresholds on day 5 ($p < 0.05$). Pain thresholds in the DEX-3 and DEX-1 groups improved

in comparison to those in the OA group following the initiation of treatment, and these improvements were sustained in both the chronic and acute -degenerative stages. These differences were statistically significant on days 10 and 21 ($p < 0.05$). Compared to the DEX-1 group, the DEX-3 group's values were significantly closer to those of the controls on day 10 ($p < 0.05$).

However, Fernandez-Cuadros *et al*., [17] compared the ozone efficacy (O2-O3) against platelet-rich plasma as IA infiltrations in KOA cases. Improvement in pain, was indicated in both groups without a significant difference (P > 0.05).

Regarding WOMACs, in group O, it was revealed that there is significant improvement in WOMAC score after IA injection of knee with ozone as WOMAC mean (±SD) 42.24 ± 4.68 before injection then significant improvement after the 4th injection with mean (±SD) 34.24 ± 4.70 and after 3 months with mean (±SD) 26.38 ± 3.39.

However, in group P, it was revealed that there is significant improvement in WOMAC score after IA injection of knee with prolotherapy as WOMAC score mean (±SD) 35.0 – 49.0 and then significant improvement after 4th injection with mean (±SD) 39.24 ± 4.70 but still less than the improvement of group O, and further improvement after 3 months with mean (±SD) 26.38 ± 3.39.

But, in group D, it was revealed that there was significant enhancement in WOMAC score after inter articular injection of knee dexametomedine as WOMAC score mean (±SD) before injection was 35.0-49.0 with significant improvement of WOMAC score after the 4th injection to become 40.24 ± 4.70 and significant improvement after 3 months with mean (±SD) 27.24 ± 4.70 but less than other two groups observed decrease in WOMAC in group O (P<0.001) (symptoms enhancement).

In concordance with the current study as well, Baygutalp *et al*., [18] The most effective method was Ozon, and both Ozon and prolotherapy were superior to exercise when evaluating WOMAC-stiffness results. Ozon was more effective than prolotherapy in reducing WOMAC-stiffness scores. In the sixth week, O was indicated to be more effective than home-based exercise in reducing WOMAC-total scores (p = 0.003, η2 = 0.166). In the 12th week, both P and O were superior to exercise with a large effect size (p = 0.023 and $p < 0.01$, respectively; η2 = 0.160), and both P and O had comparable effects.

The comparison between the two studied groups regarding K-L radiologic grading, showed that there was lower KL grade in O and P group at 3 months more than D group.

This was supported by the meta-analysis by Baygutalp *et al*., [18] who revealed that ozon and prolotherapy were associated with long-term improvement.

Regarding ROM, before injection the current study showed no significant difference in ROM knee flexion and extension between the studied groups.

After the 4th injection knee flexion and extension were significantly elevated in O group and P group (P=0.004) contrasted to group D (improvement in ROM) also after 3 months follow up.

In supporting our results, Also, Baygutalp *et al*., [18] who demonstrated enhanced ROM-passive and ROM-active scores in the sixth and twelveth weeks relative to the baseline. Ozon and protherapy were more effective than exercise in enhancing ROM-active scores when these parameters were taken into account.

Finally, according to TNF α, a little significant difference was indicated between the three groups. Ozon group before injection with a mean value of (± SD) 138.6 ± 39.63 in group O After 4th injection TNFα with a mean value of (± SD) 24.44 ± 0.27 in group O after 3 months with a mean value of (± SD) 23.40 ± 1.51 with significant decrease in biomarker serum level.

However, in Prolotherapy group before injection with a mean value of (± SD) 142.8 ± 31.38 in group P, after 4th injection TNFα with a mean value of (± SD) 24.54 ± 0.14 and after 3 months with a mean value of (± SD) 24.43 ± 0.21 with significant decrease in biomarker serum level but less than O group.

But, in group D, it was revealed that there was significant improvement in TNFα after inter articular injection of knee dexametomedine as TNFα mean (±SD) before injection was 148.5 ± 32.02 with decrease in TNFα after the 4th injection to become 24.97 ± 1.04 and after 3 months with mean (±SD) 24.87 ± 1.05.

In supporting our results Topol *et al*., [19] shows that the concentrations of synovial-fluid neurocytokine would be positively impacted by dextrose (D-glucose) injections for therapeutic purposes (dextrose prolotherapy: DPT) in painful KOA, significant decrease of an inflammatory cytokine after 3 months follow up.

We recommended that further comparative studies with larger sample size are required for generalization of these results, and longer follow-up period is needed to approve our results.

Limitations: The sample size was relatively small. The investigation was done in a single facility. The patient follow-up duration was relatively short.

Conclusions

We compared the IA ozone injection, prolotherapy or dexmedetomidine effectiveness in KOA patients. Accordingly, we indicated highly statistically significant difference between 4th injection and after 3 months follow up according to WOMAC, AROM (Flexion and Extension), Analges in each group and according to TNF-α. Ozon and prolotherapy may yield satisfactory results more than dexmedetomidine in KOA.

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Conflict of Interest

Not available

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References

1. Novakov V, Novakova O, Churnosov M. Risk factors and molecular entities of the etiopathogenesis of the knee osteoarthritis (literature review). Genij Ortopedii. 2021;27:112-120.
2. Sharma L. Osteoarthritis of the Knee. New England Journal of Medicine. 2021;384:51-59.
3. Tharakulphan S, Chaiperm C, Apivatgaroon A, Sangkomkamhang T. Analgesic efficacy of a single-dose, intraoperative, intra-articular morphine

application in ACL reconstruction. Asia Pacific Journal of Sports Medicine, Arthroscopy, Rehabilitation and Technology. 2020;20:28-31.
4. Oliviero A, Giordano L, Maffulli N. The temporal effect of intra-articular ozone injections on pain in knee osteoarthritis. British Medical Bulletin. 2019;132:33-44.
5. Raeissadat SA, Tabibian E, Rayegani SM, Rahimi-Dehgolan S, Babaei-Ghazani A. An investigation into the efficacy of intra-articular ozone (O_2-O_3) injection in cases with knee osteoarthritis: a systematic review and meta-analysis. Journal of Pain Research. 2018;11:2537-2550.
6. Sert AT, Sen EI, Esmaeilzadeh S, Ozcan E. The effects of dextrose prolotherapy in symptomatic knee osteoarthritis: A randomized controlled study. Journal of Alternative and Complementary Medicine. 2020;26:409-417.
7. Gomes LMRdS, Czeczko NG, Araújo RLTM, Cartagenes MdSdS, Barbosa Neto JO, Garcia JBS. Effect of intra-articular dexmedetomidine on experimental osteoarthritis in rats. PLOS ONE. 2021;16:245-254.
8. Devi MM, Gupta S, Amaravathi R, Udupa S, Hegde A, Ghosh S. Comparison of efficacy of intra-articular plain bupivacaine and bupivacaine with adjuvants (dexmedetomidine and magnesium sulfate) for postoperative analgesia in arthroscopic knee surgeries: A prospective, randomized controlled trial. Anesthesia: Essays and Researches. 2018;12:848-854.
9. Li H, Xie S, Qi Y, Li H, Zhang R, Lian Y. TNF-α increases the expression of inflammatory factors in synovial fibroblasts by inhibiting the PI3K/AKT pathway in a rat model of monosodium iodoacetate-induced osteoarthritis. Experimental and Therapeutic Medicine. 2018;16:4737-4744.
10. Kohn MD, Sassoon AA, Fernando ND. Classifications in brief: Kellgren-Lawrence classification of osteoarthritis. Clinical Orthopaedics and Related Research. 2016;474:1886-1893.
11. Cai Z, Cui Y, Wang J, Qi X, He P, Bu P, *et al*. A narrative review of the progress in the treatment of knee osteoarthritis. Annals of Translational Medicine. 2022;10:16-21.
12. Wang Z, Efferth T, Hua X, Zhang X-a. Medicinal plants and their secondary metabolites in alleviating knee osteoarthritis: A systematic review. Phytomedicine. 2022;6:154-159.
13. Alfieri FM, Lima A, Salgueiro M, Andrade E, Battistella LR, Silva N. Efficacy of an exercise program combined with lifestyle education in cases with knee osteoarthritis. Acta Reumatológica Portuguesa. 2020;7:53-59.
14. Xue Y, Wang X, Wang X, Huang L, Yao A, Xue Y. A comparative study of the efficacy of intra-articular injection of different drugs in the treatment of mild to moderate knee osteoarthritis: A network meta-analysis. Medicine. 2023;102:45-53.
15. Khoshbin A, Leroux T, Wasserstein D, Marks P, Theodoropoulos J, Ogilvie-Harris D, *et al*. The efficacy of platelet-rich plasma in the treatment of symptomatic knee osteoarthritis: a systematic review with quantitative synthesis. Arthroscopy: The Journal of Arthroscopic and Related Surgery. 2013;29:2037-2048.
16. Farpour HR, Ashraf A, Hosseini SS. The efficacy of ozone prolotherapy compared to intra-articular hypertonic saline injection in reducing pain and improving the function of cases with knee osteoarthritis: A randomized clinical trial. Journal of Evidence-Based Complementary & Alternative Medicine. 2021;2021:1-7.
17. Fernandez-Cuadros ME, Perez-Moro OS, Albaladejo-Florin MJ, Entrambasaguas-Estepa B, Alava-Rabasa S. Mid-term effectiveness of ozone (O_2-O_3) compared to platelet-rich plasma (PRP) in the management of knee osteoarthritis: A randomized parallel controlled trial. Middle East Journal of Rehabilitation and Health Studies. 2019;6:66-74.
18. Baygutalp F, Çelik M, Öztürk MU, Yayık AM, Ahıskalıoğlu A. Comparison of the efficacy of dextrose prolotherapy and ozone in cases with knee osteoarthritis: A randomized cross-sectional study. Applied Sciences. 2021;11:9991-9999.
19. Topol GA, Pestalardo IG, Reeves KD, Elias F, Steinmetz NJ, Cheng A-L, *et al*. Dextrose prolotherapy for symptomatic grade IV knee osteoarthritis: A pilot study of early and longer-term analgesia and pain-specific cytokine concentrations. Clinical Practice. 2022;12:926-938.

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