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# Comparative study between intra articular injection of ozone with corticosteroids versus plasma rich in growth factors in limitation of pain in knee osteoarthritis

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**Abstract**
**Background:** Knee osteoarthritis (OA) represents a common degenerative disorder, characterized by a functional limitations due to chemical as well as mechanical stress on joint, leading to discomfort along with reduced range of motion (ROM). This work was aimed at comparing the ozone intra-articular injections' effectiveness with corticosteroids versus PRGF as regards pain improvement in knee OA patients.
**Methods:** Our prospective randomized double-blind study involved 90 cases aged from 21 to 65 years old, both sexes, diagnosed with stage 2-3 knee OA and having symptoms of Knee OA at least 3 months after getting usual conservative treatment. Cases underwent a random and equal categorization into two groups. Group O: were administered ozone with corticosteroids IA injections while Group P: were administered PRGF IA injections.
**Results:** In first month after intra articular injection, both visual analogue scale (VAS) as well as Western Ontario and McMaster Universities OA score (WOMACs) showed significantly decrease within group O as opposed to group P ($p$<0.001). Also, patients required for oral analgesics within group O exhibited less values as opposed to group P ($p$<0.001) with improvement of both flexion and extension within group O as opposed to group P. Six months after intra articular injection, both VAS and WOMACs showed significantly decrease within group P as opposed to group O ($p$<0.001). Also, cases required for oral analgesics within group P was less as opposed to group O ($p$<0.001) with improvement as regards both flexion and extension within group P as opposed to group O ($p$<0.001) and improvement of KL classification within group P as opposed to group O ($p$<0.001).
**Conclusions:** Both intra articular injection of ozone with corticosteroids and PRGF were safe and effective in limiting pain in knee OA. Ozone plus corticosteroids could result in favorable short-term outcomes as opposed to PRGF.

**Keywords:** Osteoarthritis, intra articular injection, ozone, corticosteroids, plasma rich in growth factors

## Introduction
Knee osteoarthritis (OA) represents a common degenerative disorder, characterized by a functional limitations due to chemical as well as mechanical stress on joint, leading to discomfort along with reduced range of motion (ROM) [1].
OA has several underlying etiolohies, involving mechanical trauma, obesity, hereditary factors, inflammatory joint disorders, prior joint infections, aging, metabolic variables, osteoporosis, as well as ligamentous laxity [2].
Various approaches have been proposed for such a condition, involving patient education, pharmacological intervention, exercise prescription, physical as well as conventional agent techniques like pulsed radio-frequency, along with surgical procedures. However, the current therapeutic options for knee OA exhibits less effectiveness or satisfaction for cases, with at least forty percent addressing pain. Also, old age prevalence of knee OA make treatment with analgesics has several side effects over stomach, liver and kidney and also surgical one has high morbidities and mortalities for old ages [3].
Among these methods, injections administered intra-articularly. Several products have been utilized, involving corticosteroids, dextrose, hyaluronic acid (HA), platelet-rich plasma (PRP), plasma rich-in growth factors (PRGFs), ozone and Others [4].

Among These modalities of intra-articular injections, Autologous PRP has been a prominent choice for managing cases developing knee OA. Multiple research addressed the PRP injections' efficacy for knee OA [3], since PRP may act as an analgesic and promote cell growth. The PRP intra-articular injection can modify the joint environment, enhance chondrogenesis, along with preventing knee joint damage by decreasing the pro-inflammatory mediators' production through the high concentrations of biological molecules as well as growth factors found in platelet granules. This process may help reverse the catabolic environment in OA, restore joint homeostasis, as well as promoting the damaged cartilage repair [5].

Nevertheless, there is a lot of issues as regards the increased intra-articular PRP usage while managing knee OA within clinical practice [6]. Biologic activators are utilized for stimulating platelets to produce their granular content, creating PRGF, which represents the PRP's end, devoid of leukocytes as well as inflammatory cytokines, while containing a precise quantity of cytokines along with growth factors [4-7].

In recent times, there has been increasing interest in utilizing ozone as a safe therapeutic option for managing cases developing knee OA. Evidence shows that injecting a combination of oxygen along with ozone intra-articularly may enhance mild to moderate knee OA[3]. Yet, Combining it with corticosteroids may result in a slightly improved short-time and prolonged outcome, since corticosteroids has anti-inflammatory and immunosuppressive effects either intra-articular or systemic

This work was aimed at comparing the ozone intra-articular injections' effectiveness with corticosteroids versus PRGF as regards pain improvement in knee OA patients.

## Patients and Methods

Our prospective randomized double-blind study involved 90 patients whose ages fell between 21 and 65 years, both sexes, developing stage 2-3 knee OA based on the Kellgren-Lawrence Classification System (K-L) [8], Western Ontario and McMaster Universities (WOMAC) Score > 2 for pain stiffness as well as physical disabilities [9] Additionally, they exhibited = symptoms of Knee OA at least 3 months after getting usual conservative treatment like oral analgesics and therapeutic exercises. The study was done from June 2022 to May 2023 following the Ethical Committee's approval Tanta University Hospitals, Tanta, Egypt (approval code: 35293/2/22) and registration on clinicaltrials.gov (ID: NCT05837494). Participants were allowed to sign an informed consent.

We excluded cases developing stage 1 or 4 OA following K-L classification, prior knee trauma in the previous month, malignancies, any surgical intervention of the knee, local or systemic infection and bleeding disorders.

### Randomization and blinding

The patients underwent a random an equal categorization into two groups. The categorization process was accomplished utilizing computer generated random numbers as well as closed opaque envelopes: Group O: were administered ozone with Corticosteroids intra-articular injection while Group P: were administered a PRGF intra-articular injection.

### Group O: Intra-Articular injection with Ozone and corticosteroids

Patients received one session weekly with around 4 intra-articular knee injection sessions with combination of 5ml (25µg/ml) ozone injection + 2 ml lignocaine 2% + 2 ml Betamethasone sodium phosphate 4 mg [10]. Under aseptic precautions. Inserting a 22-G needle was carried out inferior-laterally into infra-patellar pouch, injecting 2 ml of 4 mg Betamethasone sodium phosphate combined with 2 ml of lignocaine 2% done slowly (Over 1–2 minutes). A needle was kept in-place while administering a five milliliters of ozone at 25µg/ml. Cases were instructed to stop vigorous physical activities for two to three days after the intra-articular injection. Figure 1, 2

**Fig 1:** Ozone Concentrator Device.

### Group P: Intra-Articular injection with PRGF Method

Patients received two doses with 2 weeks interval by injection of prepared PRGF vial intra-articularly.

### Preparation of PRGFs

Platelets were obtained from separate whole blood donors by apheresis technique. Seronegative plasma underwent nucleic acid testing then subjected to viral/pathogen inactivation utilizing Ultraviolet-radiation as well as riboflavin treatment via the Mirasol system. Platelets within buffy coat layer were stimulated with CaCl2 to evacuate their growth factors. The buffy coat layer underwent many rounds of filtering in a specialized ultrafiltration process to remove excess water, low-molecular-weight molecules, cellular components, as well as fibrinogen. This process resulted in the remaining GFs being ultra-concentrated An automated aseptic procedure was utilized for dispensing a fluid filtrate in predefined amounts standardized to match the platelet content produced by a 20 ml of whole blood, with a platelet count of 1 million per µl. The filtrate containing mostly platelet-derived GFs was lyophilized.

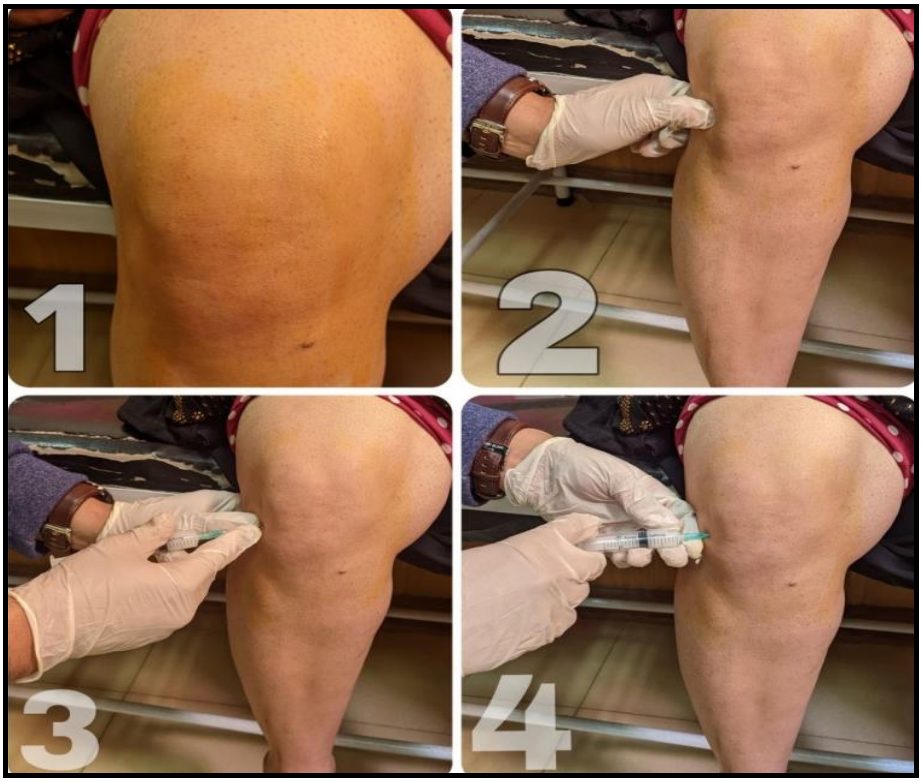



**Fig 2:** (1) sterilization of knee (2) Palpation of infra-patellar pouch (3) placement of needle (4) Injection

The end product underwent aerobic as well as anaerobic testing for microorganisms before release. L-GFs are provided as lyophilized cake within a firmly-sealed container then kept at 2–8 °C [11].

Before being utilized, the product was reconstituted utilizing a mixture of one ml of saline along with one ml of lignocaine 2%. A gentle vial rubbing was then employed for three minutes. Thereafter, it was left at room temperature for 5 minutes to fully rehydrate the protein [12]. The mixture was injected utilizing 22-G needles into the infra-patellar pouch after administering appropriate disinfectants. The second injection was administered two weeks later to evenly distribute the injected fluid throughout the synovial region. Cases were instructed to avoid intense exercise for two to three days after the intra-articular injection. Figure 3.

All measurement recorded after one week, one month, three months, six months following injection based on:

**The Visual Analogue Scale (VAS)**

Represents a subjective scale utilized for a quantitative pain assessment, falling between zero and ten. Zero exhibits pain absence, while ten exhibits severe pain [13].

**The Western Ontario and McMaster Universities (WOMAC) index**

Represents an English-language questionnaire created and confirmed by Bellamy *et al*. The self-administered composite questionnaire has five items on pain, two on stiffness, as well as seventeen on the difficulty level as regards everyday tasks. It was translated into Arabic to ensure its validity [9].

**Dose of analgesics required for pain control before and after injections:** One week before injections all patients was given etoricoxib 60 mg orally once daily and if pain was not controlled on this dose etoricoxib dose increased to 90 mg per day orally, if pain was still patient added paracetamol 665 mg once daily orally up to 3 times per day till patient reached satisfactory level of pain control, analgesic type and dose had been recorded, patients continued on these analgesia till the end of injection sessions, after last injection the dose of analgesia reduced gradually on opposite way till the patient reach the same satisfactory level of pain control before injection then the doses of analgesics was recorded.

**Kellgren-Lawrence Classification System (K-L) [8]**

Which classify knee OA by radiological finding into 4 stages: [Grade 1 Uncertain or doubtful joint space narrowing as well as potential osteophytic lipping, Grade 2: clear osteophytes present with potential joint space reduction. Grade 3 (Moderate): presence of many osteophytes, clear joint space narrowing, some sclerosis, as well as potential bone ends' deformity. Grade 4 (Severe): prominent bone spurs, significant joint space reduction, severe sclerosis, along with clear bone ends' deformity.

**Range of motion (ROM) using universal goniometer**

Normal ROM of knee joint varies from 0◦ in fully extended knee to 135◦ in fully flexed knee which measured by universal goniometer [14].

The primary outcome were improvement of knee OA pain according to VAS, representing a subjective scale utilized for a quantitative pain assessment, falling between zero and ten. Zero exhibits pain absence, while ten exhibits severe pain [13] and decrease of analgesic requirement for pain control after injection. The secondary outcomes were improvement of joint ROM and decrease stiffness, improvement of knee joint cartilage regeneration by K-L System [8] and improvement of life style according to WOMAC Evaluation [9].

**Sample size calculation**

The sample size as well as power analysis were measured utilizing Epi-Info software statistical package created by

World Health organization and center for Disease Control and Prevention, Atlanta, Georgia, USA version 2002 [15]. The criteria utilized for calculating sample size involved the following: [95% confidence limit, 80% power of the study as well as expected pain control within favorable treatment group between 90% of cases as opposed to 65% within least favorable treatment group].

The sample size based on the previously mentioned criteria was found at N>44 in each group. The researcher will increase the sample size to 45 to compensate for incomplete results.

**Statistical analysis**

Data was sent to the computer then underwent an analysis utilizing IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp).

Qualitative data were displayed utilizing numbers as well as percentage. The Shapiro-Wilk test was employed for verifying the normality of distribution Quantitative data were displayed utilizing range (minimum and maximum), mean, SD, median as well as interquartile range (IQR). The results' level of significance was set to 5%.

**Results**

Regarding out research, 102 cases were tested for eligibility, eight cases were not matched with inclusion requirements (five cases exhibited knee inflammation with effusion while three cases developed coagulopathy) as well as four cases disagreed to participate in our research Fig 3.

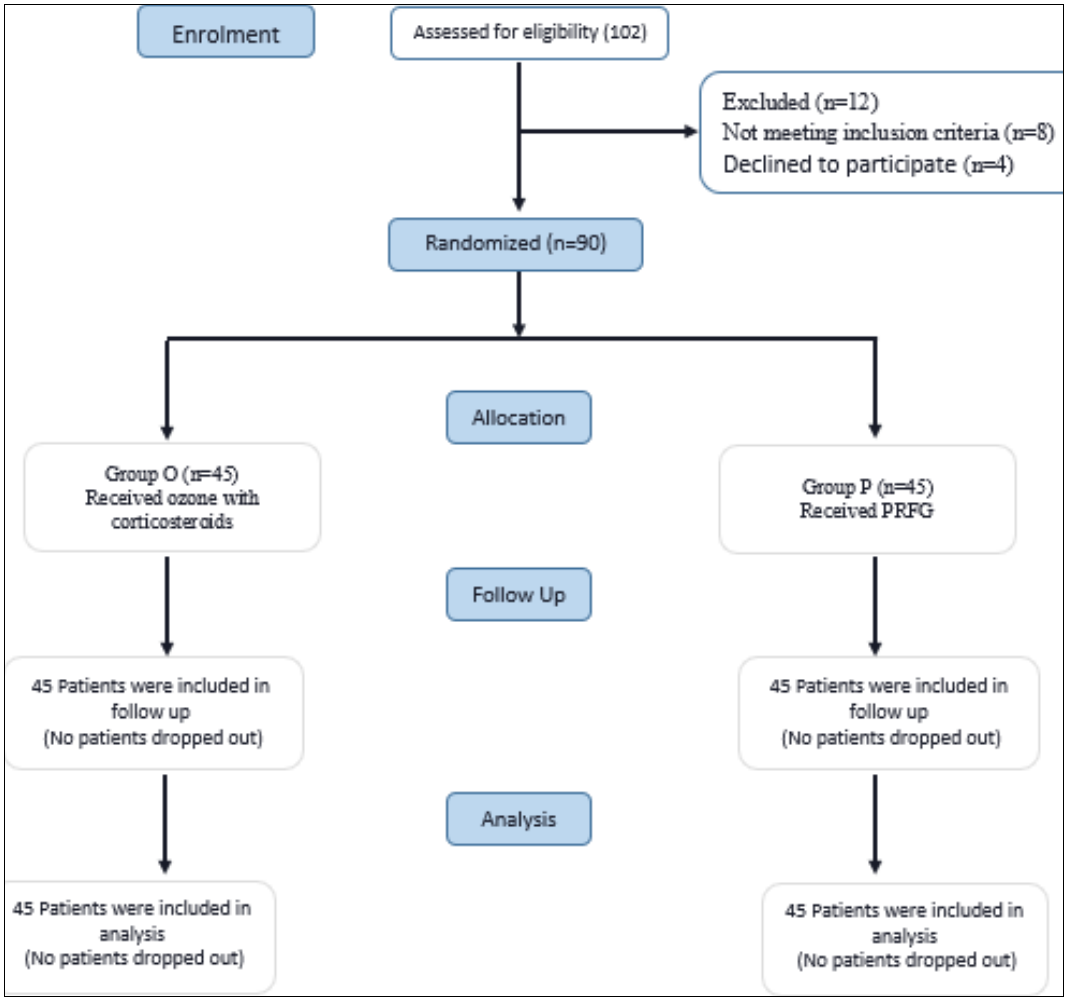



**Fig 4:** Flow chart of the studied groups

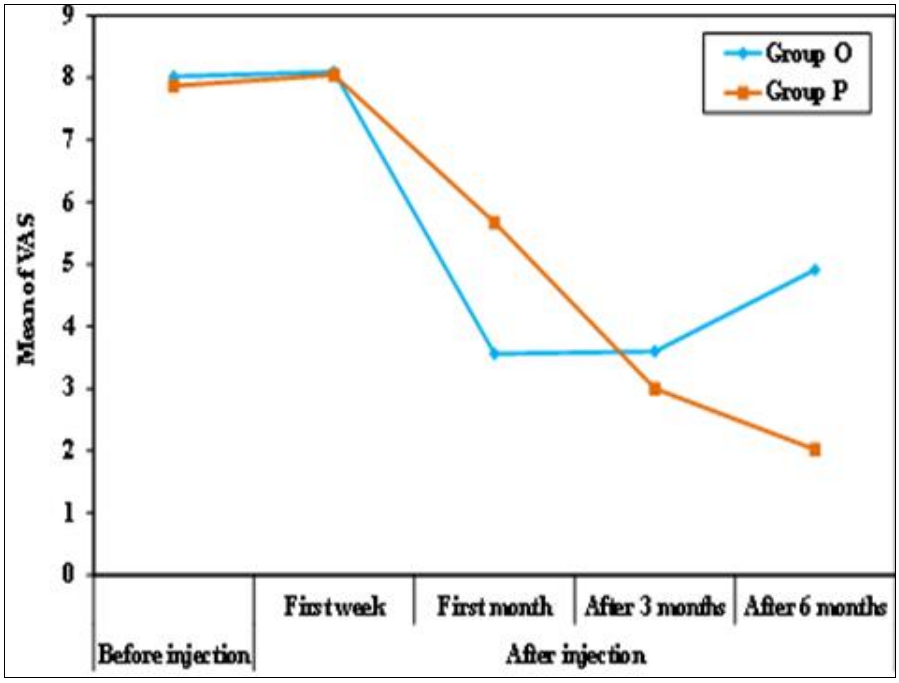
Demographic data showed no statistically significant variations among both groups. Table 1

**Table 1:** Comparison among both groups based on demographic data

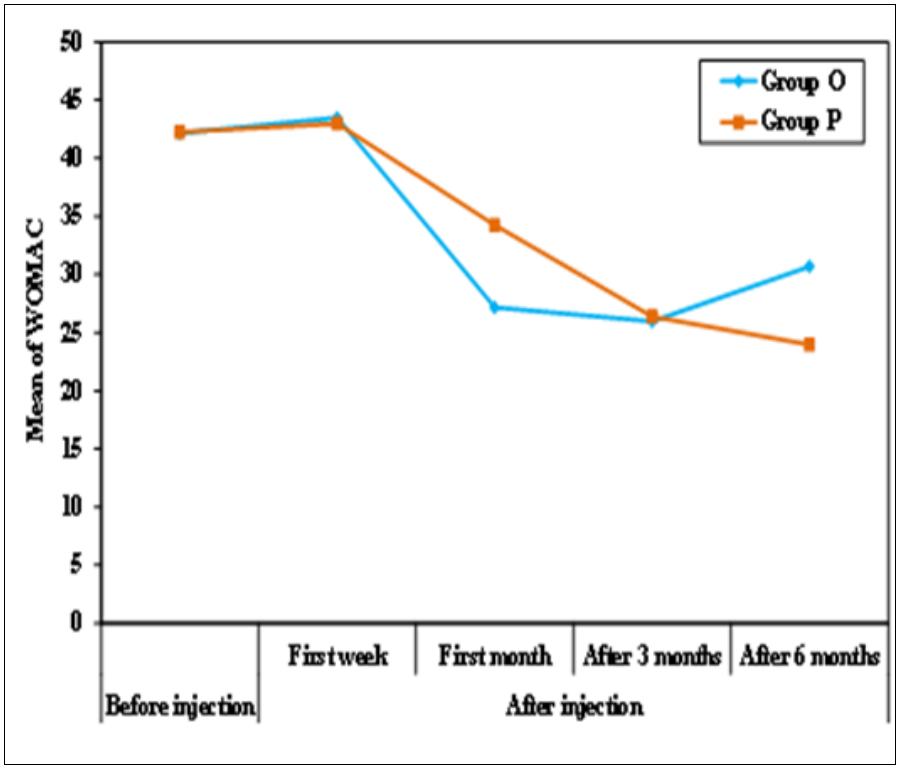
| | | Group O (n = 45) | Group P (n = 45) | p |
|---|---|---|---|---|
| Age (years) | | 48.51±7.87 | 48.09±9.53 | 0.819 |
| Sex | Male | 17 (37.8%) | 16 (35.6%) | 0.827 |
| | Female | 28 (62.2%) | 29 (64.4%) | |
| Weight (kg) | | 97.44±4.30 | 97.38±4.96 | 0.946 |

Data are displayed as mean ± SD or frequency (%).

After first month VAS and WOMACs showed statistically significant decrease within Group O as opposed to group P, but VAS after three and six months showed statistically significant decrease within Group P as opposed to group O. while WOMACs score after six months showed statistically significant decrease within Group P as opposed to group O Fig 2.




A)




B)

**Fig 5:** Comparison among both groups based on (A) visual analogue scale (VAS) as well as (B) Western Ontario and McMaster Universities OA score (WOMACs)

Following one week of injection, using analgesic drugs showed no significant variation among both groups (P=0.284). After one month, a statistically significant variation was documented among both groups ($p$<0.001) as patients required for oral analgesia in group O were less than patients required for oral analgesia in group P. After 3 months, a statistically significant variation was documented among both groups ($p$<0.001) as patients requiring oral analgesia in group O were less than patients required for oral analgesia in group P but with better improvement in group P in comparison to the first month. On the other hand, following a period of six months, a statistically significant variation was documented among both groups ($p$<0.001). As patients required for oral analgesia in group P were less than patients required for oral analgesia in group O. Table 2

**Table 2:** Comparison among both groups based on analgesic requirement

| | | Group O (n = 45) | Group P (n = 45) | p |
|---|---|---|---|---|
| First week | Et 90 | 16 (35.6%) | 21 (46.7%) | 0.284 |
| | Et 90 pr665 | 29 (64.4%) | 24 (53.3%) | |
| First month | Nil | 19 (42.2%) | 0 (0.0%) | <0.001* |
| | pr665 | 14 (31.1%) | 0 (0.0%) | |
| | Et 60 | 6 (13.3%) | 21 (46.7%) | |
| | Et 90 | 3 (6.7%) | 23 (51.1%) | |
| | Et 90 pr665 | 3 (6.7%) | 1 (2.2%) | |
| After 3 months | Nil | 12 (26.7%) | 0 (0.0%) | $^{MC}$p <0.001* |
| | pr665 | 21 (46.7%) | 20 (44.4%) | |
| | Et 60 | 7 (15.6%) | 25 (55.6%) | |
| | Et 90 | 3 (6.7%) | 0 (0.0%) | |
| | Et 90 pr665 | 2 (4.4%) | 0 (0.0%) | |
| After 6 months | Nil | 1 (2.2%) | 20 (44.4%) | $^{MC}$p <0.001* |
| | pr665 | 17 (37.8%) | 25 (55.6%) | |
| | Et 60 | 18 (40.0%) | 0 (0.0%) | |
| | Et 90 | 6 (13.3%) | 0 (0.0%) | |
| | Et 90 pr665 | 3 (6.7%) | 0 (0.0%) | |

Data are displayed as frequency (%). MC: Monte Carlo, *: Statistically significant at $p \leq 0.05$, Nil: no oral analgesia, Et 60: Etoricoxib 60 mg once daily orally, Et 90: Etoricoxib 90 mg once daily orally, pr665: Paracetamol 665mg once daily orally, Et 90 pr665: Etoricoxib 90 mg combined with Paracetamol 665mg once daily orally.

After first week, first month and 3 months, no statistically significant different was documented among both groups based on KL classification (P>0.05). Yet, following a period of six months, a statistically significant different was documented among both groups ($p$<0.001) with marked improvement within group P as opposed to group O. Table 3

**Table 3:** Comparison among both groups based on KL classification

| | | Group O (n = 45) | Group P (n = 45) | P |
|---|---|---|---|---|
| First week | Grade 1 | 0 (0.0%) | 0 (0.0%) | 0.824 |
| | Grade 2 | 16 (35.6%) | 15 (33.3%) | |
| | Grade 3 | 29 (64.4%) | 30 (66.7%) | |
| First month | Grade 1 | 0 (0.0%) | 0 (0.0%) | 1.000 |
| | Grade 2 | 16 (35.6%) | 16 (35.6%) | |
| | Grade 3 | 29 (64.4%) | 29 (64.4%) | |
| After 3 months | Grade 1 | 0 (0.0%) | 0 (0.0%) | 0.389 |
| | Grade 2 | 16 (35.6%) | 20 (44.4%) | |
| | Grade 3 | 29 (64.4%) | 25 (55.6%) | |
| After 6 months | Grade 1 | 3 (6.7%) | 20 (44.4%) | <0.001* |
| | Grade 2 | 20 (44.4%) | 25 (55.6%) | |
| | Grade 3 | 22 (48.9%) | 0 (0.0%) | |

Data are presented as frequency (%). *: Statistically significant at $p \leq 0.05$, KLs: Kellgren and Lawrence classification, Grade 1: Doubtful, Grade 2: Minimal, Grade 3: Moderate

Before injection, first week and 3 months in flexion and extension exhibited no statistically significant variation among both groups (P=0.799). After the first month, a statistically significant variation was documented among both groups (P=0.004) as knee flexion and extension improved in group O than group P, while following a period of six months, a statistically significant variation was documented among both groups ($p$<0.001) as knee flexion and extension improved in group P than group O. Table 4

**Table 4:** Comparison among both groups based on ROM (Flexion and extension) as measured by goniometry

| | | Group O (n = 45) | Group P (n = 45) | p |
|---|---|---|---|---|
| **ROM (Flexion)** | | | | |
| Before injection | | 123.02±5.04 | 122.89±4.70 | 0.799 |
| After injection | First week | 121.4±4.49 | 123.27±4.58 | 0.051 |
| | First month | 130.3±1.68 | 126.62±3.68 | 0.004* |
| | After 3 months | 130.3±1.68 | 131.04±2.40 | 0.056 |
| | After 6 months | 125.4±1.98 | 133.42±1.48 | <0.001* |
| **ROM (Extension)** | | | | |
| Before injection | | 14.93±3.56 | 15.09±3.13 | 0.773 |
| After injection | First week | 14.84±2.92 | 15.36±2.76 | 0.359 |
| | First month | 4.78±3.46 | 12.38±1.71 | <0.001* |
| | After 3 months | 6.09±2.19 | 6.44±1.08 | 0.306 |
| | After 6 months | 9.73±2.25 | 1.33±1.04 | <0.001* |

Data are displayed as mean ± SD. *significant p value <0.05, ROM: range of motion.

## Discussion

OA represents a degenerative joint condition, with gradual articular cartilages' resorption and breakdown. KOA often occurs as a result of tear as well as wear induced through aseptic articular cartilage inflammation [16]. Approximately 250 million individuals worldwide are affected with knee osteoarthritis (KOA) based on epidemiological surveys. The KOA incidence is increasing, making it a significant global public health issue [17]. The KOA cases often suffer from knee pain, as well as restricted movement. Additionally, in severe instances, disabilities might occur. These adverse events affect their quality of life [18].

Our research addressed, the pain improvement based on VAS was better in ozone group at short-term (1 month post injection), but at long term (6-months post injection) the improvement was better in PRGF group. Supporting our findings, Raeissadat *et al*. [3] compared the short-term as well as prolonged outcomes as regards the intra articular-injection of HA, PRP, PRGF, as well as ozone among KOA cases. Also, a recent network meta-analysis including 16 RCTs. It involved 1652 patients by Xue *et al*. [19] addressed, the most effective methods for reducing VAS scores were IA injection of PRP-derived GFs (surface under the cumulative ranking area [SUCRA] 84.9%) and HA and PRP (SUCRA 84.9%).

The comparison between the studied groups addressed no significant variations among both studied groups before injection, 1 week and 3 months following injection ($p>0.05$ for all). But at 1 month, a significant variation was documented between two groups with observed decrease in WOMAC in group O ($p<0.001$) (improvement of symptoms). Following six months, a significant variation was documented among both groups with observed decrease in WOMAC within group P ($p<0.001$) (improvement of symptoms). Our findings showed that the improvement WOMAC was better in ozone group at short-term (1 month post injection), but at long term (6-months post injection) the improvement was better in PRGF group. Supporting our findings, Raeissadat *et al*. [3] revealed that at a two-months periof following the injection, the ozone group exhibited a reduced WOMAC values, (better results) in comparison with HA, PRP as well as PRGF, groups. Significant variations were documented as regards WOMAC (For Total score and Pain and Function sub-scores). Nevertheless, at a six-months follow-up period, cases managed using HA, PRP, PRGF exhibited improved findings as regards WOMAC in comparison with others using ozone. At such a stage, the WOMAC (Total, and Pain and Function sub-scores) exhibited significantly greater values within ozone group as opposed to other groups ($p< 0.05$). As well, Gaballa *et al*. [20] revealed that PRP as well as ozone IA injections lead to significant enhancement as regards WOMAC at 1 as well as 3 months compared to baseline. The improvement was higher in intra-articular injection of PRP group at both 1 and 3 months.

Our findings also addressed, a higher reduction was documented as regards pain score and analgesic requirement in ozone group at short-term (1-month post injection), but at long term (3 and 6-months post injection) there was higher reduction in pain score and analgesic requirement in PRGF group. Supporting out findings, Raeissadat *et al*. [3] and Xue *et al*. [19] showed that PRGF injections have the best long-term outcome in terms of pain reduction, and consequently reduction in analgesic requirement compared to other treatment modalities including ozone injection. Also, Gaballa *et al*. [20] and Duymus *et al*. [21] addressed, PRP injection have better long-term outcome in terms of pain reduction, and consequently reduction in analgesic requirement compared to ozone injection.

When comparing both studied groups based on KL radiologic grading, lower KL grade was documented in PRGF group following a six-months period but no significant variation was observed among groups as regard KL at 1 week, 1 and 3 months follow up. Indicating better long-term outcome in PRGF group. This was supported by the meta-analysis by Xue *et al*. [19] addressing, PRGF was associated with better prolonged outcomes as opposed to ozone treatment.

After one month knee flexion exhibited significantly greater values within O group in comparison with P group ($P=0.004$) (improvement in ROM). However, knee extension exhibited significantly greater values within P group as opposed to O group (Deterioration in ROM). Which mean ROM showed improved results within group O as opposed to group P. After three months, no significant variations were documented as regards ROM knee flexion as well as extension among groups. After six months, knee flexion exgubuted significantly greater values within P group in comparison with O group (improvement in ROM). However, knee extension exhibited significantly greater values within O group as opposed to P group (deterioration in ROM). Which mean ROM exhibited an improvement within group P as opposed to group O. Meanwhile, some statistically significant variations were documented as regards ROM among groups, these differences were clinically non-significant. However, Ismaiel *et al*. [22] showed that Flexion deformity and extension lag decreased for PRP and corticosteroid injections groups after injection, with significant differences between groups at 6 months; however, no significant variation was documented among groups at one as well as three months, at time- point for flexion deformity and extension lag, respectively.

## Limitation

Limitations of this study included a relatively modest sample size. It was a single-center study. The lack for control group and relatively short follow up period. Further comparative research involving more participants and longer follow-up are required for confirming our findings along with detecting the best treatment modality.

## Conclusions

Both intra articular injection of Ozone with Corticosteroids and PRGF were safe and effective in limitation of pain in knee OA. Ozone plus corticosteroids could result in favorable short-term outcomes in comparison with PRGF; But PRGF could show an improvement as regards KOA symptoms plus improvement of cartilage regeneration with time in comparison with ozone along with corticosteroids. Hence, such products appear to be the most suitable options for prolonged treatment.

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Nil.

**Conflict of Interest**

Nil.

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