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EFFICACY OF PLATELET-RICH PLASMA INJECTION VERSUS OXYGEN-OZONE THERAPY FOR THE TREATMENT OF KNEE OSTEOARTHRITIS : A META-ANALYSIS AND SYSTEMATIC REVIEW

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ABSTRACT

Introduction. Knee osteoarthritis (KOA), a degenerative knee condition, represents a major Indonesian public health issue because it consistently damages patients' quality of life. Recent studies have explored the intra-articular injection of platelet-rich plasma and oxygen-ozone therapy as potential treatments for knee osteoarthritis. This review aimed to evaluate the effect of platelet-rich plasma (PRP) injection compared to oxygen-ozone therapy for treating knee osteoarthritis patients. **Method.** The reporting methodology of this work followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards. A literature search was conducted through PubMed and Google Scholar by combining several keywords, including PRP Injection with oxygen-ozone therapy for patients affected by KOA. The Cochrane Risk of Bias 2 (ROB 2) tool was employed to assess the risk of bias. **Result&Analysis.** The meta-analysis included 251 participants from these 4 Randomized Controlled Trials (RCTs). The results indicated no statistically significant difference between PRP injection and oxygen-ozone therapy in terms of the visual analog scale score and the mean difference in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale at the 1-month follow-up. However, a significant difference was observed between the two interventions in the WOMAC subscales for stiffness and physical function. **Discussion.** This meta-analysis shows that KOA patients might achieve better pain relief together with improved function outcomes from PRP injections than from oxygen-ozone therapy based on joint stiffness and functionality WOMAC scores.

Keywords: Platelet-Rich Plasma, Oxygen-Ozone Therapy, Knee Osteoarthritis, WOMAC scores, osteoarthritis.

INTRODUCTION

Knee osteoarthritis (KOA) is a highly widespread degenerative joint illness that substantially impacts mobility, quality of life, and socioeconomic productivity in the elderly population. Knee osteoarthritis, marked by gradual cartilage deterioration, subchondral bone remodeling, and persistent inflammation, presents a significant burden on individuals and global healthcare systems. KOA constitutes an escalating public health issue in Indonesia and the ASEAN area, where rapid population aging, increasing obesity, and changing lifestyle variables interact to heighten disease burden and functional impairment.(Chen et al., 2025; Wu et al., 2025) Knee OA leads to decreased life quality among patients and may qualify as a major health issue affecting the public at large. The medical condition causes destructive effects on performance levels in patients.(Butarbutar et al., 2024)

The management of KOA is based on a multimodal, stepwise approach that prioritizes conservative, nonoperative therapies prior to contemplating surgical intervention. Fundamental nonpharmacologic interventions encompass patient education, weight loss for persons with excess weight, organized exercise regimens (aerobic conditioning, strength training, and range-of-motion exercises), and the utilization of assistive devices or braces to alleviate joint stress and enhance functionality. Pharmacologic therapies are generally commenced or supplemented with foundational interventions, starting with acetaminophen for mild-to-moderate pain and progressing to nonsteroidal anti-inflammatory drugs (NSAIDs) when analgesia is insufficient or inflammation is significant, while considering cardiovascular, renal, and gastrointestinal risk factors.(Shtroblia et al., 2025) Intra-articular therapies, such as corticosteroid injections and hyaluronic acid (viscosupplementation), are utilized as specific symptom-relief measures, especially for exacerbations or localized synovitis; however, evidence for long-term disease modification is scarce, and guideline recommendations differ by region and healthcare system context.(Maqbool et al., 2021)

In recent years, regenerative and minimally invasive therapies have surfaced as appealing alternatives to traditional treatments for KOA. Platelet-rich plasma (PRP) injection and oxygen–ozone (O_2–O_3) therapy are two biologically based methods designed to modify the intra-articular environment and facilitate tissue repair. These bioactive molecules have been demonstrated to enhance chondrocyte proliferation, stimulate extracellular matrix synthesis, and reduce inflammatory cytokines within the joint, contributing to cartilage regeneration and pain relief.(Sconza et al., 2020)

Consequently, although the utilization of platelet-rich plasma and oxygen–ozone therapy as non-surgical interventions for knee osteoarthritis is increasing, their comparative efficacy remains uncertain owing to diverse study designs, limited sample sizes, and variable outcome measures in published research. A rigorous synthesis of the available evidence is needed to clarify their comparative effectiveness on pain reduction, functional improvement, and safety, and to inform clinical decision-making in routine orthopaedic practice. This systematic review and meta-analysis seeks to quantitatively evaluate the effectiveness of platelet-rich plasma injection compared to oxygen–ozone therapy for treating knee osteoarthritis, offering updated, evidence-based recommendations for orthopedic surgeons and other clinicians addressing this common degenerative joint condition.

METHOD AND ANALYSIS

The reporting methodology of this work followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards (Figure 1) and no ethical clearance was needed due to study requirements.(Moher et al., 2015) This review article's protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the protocol registration number CRD420251128170.

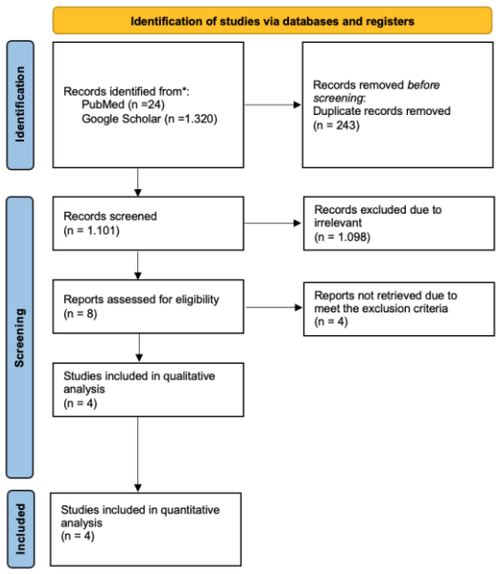

Figure 1 PRISMA Flow Diagram

A literature search was conducted through PubMed and Google Scholar by combining several keywords, including PRP Injection with Ozone Therapy for patients affected by KOA. The review question for included studies followed a population, intervention, comparison, results and study design (PICOS) framework by defining (i) study participants as individuals with KOA and (ii) PRP Injections as the intervention of interest, while (iii) Ozone therapy served as the comparator and (iv) Visual Analog Scale (VAS) scores together with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for pain along with stiffness and physical function as the primary outcomes and RCTs as the preferred study design. This study evaluated papers through three specific screening criteria: (i) Papers had to comply with PICOS standards, (ii) All articles needed to be written in English and (iii) Researchers had to have access to the full text of selected articles. Research classified as systematic reviews with or without meta-analysis as well as literature reviews, case reports, case series and non-human subject studies, including in vitro investigations and abstracts, conference proceedings, editorials and author comments, were excluded from the study. The literature search took place in November 2024 while adhering to a restriction that research should span no more than ten years. All database search results transferred to Rayyan.ai operated as the selection system. [10] Our research team, consisting of two independent reviewers, screened the titles and abstracts first before performing a full-text assessment for eligibility. Writers jointly addressed conflicts that developed during the paper selection phase.

Two independent researchers conducted a standardized data extraction process, which gathered necessary clinical outcomes for quantitative assessments across all studied trials. Researchers extracted various data points from the included studies, including publication year, research design, patient numbers, participant ages as well as pain data from VAS and WOMAC. The authors conducted discussions with all other authors whenever they encountered extraction-related disagreements.

The Cochrane Risk of Bias 2 (ROB 2) tool was employed for the risk of bias assessment.(Sterne et al., 2019) The assessment rated each domain to have a "low risk," "unclear risk," or "high risk" bias level. Two reviewers conducted independent risk of bias evaluations, which required discussion with fellow authors following any differing grades.

A quantitative analysis of the included studies was conducted with Review Manager 5.4 employing 95% confidence intervals (CI). We used pooled risk ratio analysis to determine dichotomous outcomes. Mean Difference produced outcome calculations for continuous variables through random effects model (REM) or fixed effects model (FEM).

RESULT

The database search through PubMed and Google Scholar yielded 1.344 articles. Following an initial check for duplication through Rayyan. ai service researchers reviewed the title and abstract for irrelevant content. A review of 8 articles through full-text screening took place after title and abstract screening. A quantitative evaluation through meta-analysis was performed in 4 studies from the literature review.

Table 1 summarizes all included RCTs comparing the efficacy of PRP injection and Oxygen-Ozone Therapy in treating KOA. The studies were conducted in Turkey and Spain between 2016 and

2020, with sample sizes ranging from 49 to 80 patients. The mean age of participants across the studies was approximately 56 to 65 years, indicating a focus on middle-aged to older adults, a demographic commonly affected by KOA. The risk of bias assessment was conducted using the Cochrane RoB 2. The presence of methodological limitations and varying levels of risk of bias across the trials underscores the need for more rigorously designed studies, as shown in Figure 2.

Table 1 Characteristics of included studies

Study, Country (year)	Study design	Number of patients		Age (Mean ± SD)		VAS Score (Mean ± SD)	WOMAC Score (Mean ± SD)
		PRP Injection	Oxygen-Ozone Therapy	PRP Injection	Oxygen-Ozone Therapy		
(Duymus et al., 2017)	Randomized Controlled trial	33	35	60.4 ± 5.1	59.4 ± 5.7	**PRP Injection :** 2.5 ± 0.7 **Oxygen-Ozone Therapy :** 3.5 ± 1.5	**PRP Injection** **Pain :** 6.8 ± 1.8 **Stiffness :** 2.8 ± 0.8 **Function :** 19.7 ± 7.1 **Oxygen-Ozone Therapy** **Pain :** 6.6 ± 3.5 **Stiffness :** 2.7 ± 1.6 **Function :** 21.7 ± 8.6
(Yeprem et al., 2018)	Randomized Controlled trial	40	40	56.7		**PRP Injection :** 2.08 ± 1.75 **Oxygen-Ozone Therapy :** 2.41 ± 1.7	**NR**
(Fernandez-Cuadros et al., 2019)	Randomized Controlled trial	27	27	58.03 ± 10.31	65.36 ± 11.02	**PRP Injection :** 2.96 ± 1.53 **Oxygen-Ozone Therapy :** 2.14 ± 2.07	**PRP Injection** **Pain :** 5.55 ± 2.62 **Stiffness :** 0.4 ± 0.63 **Function :** 15.25 ± 12.38 **Oxygen-Ozone Therapy** **Pain :** 4.03 ± 3.97 **Stiffness :** 0.92 ± 0.99 **Function :** 16.4 ± 12.48

(Yalçın, 2020)	Randomized Controlled trial	25	24	53.6 ± 8.2	53.2 ± 7.7	**PRP Injection :** 1.1 ± 0.8 **Oxygen-Ozone Therapy :** 3.1 ± 1.3	**PRP Injection** **Pain :** 1.9 ± 1.5 **Stiffness :** 0.4 ± 0.6 **Function :** 5.8 ± 5.7 **Oxygen-Ozone Therapy** **Pain :** 7.0 ± 3.3 **Stiffness :** 0.7 ± 0.6 **Function :** 9.9 ± 5.9

PRP, platelet-rich plasma; VAS, Visual Analog Scales; WOMAC, the Western Ontario and McMaster Universities Osteoarthritis Index; NR, not reported

Figure 2 Risk of Bias assessment based on RoB 2 tools

The mean VAS score differences between PRP injection recipients and oxygen-ozone therapy subjects revealed -0.68 points (MD: -0.68; 95% CI: -1.72, 0.36; P = 0.20) with substantial variability (I2 = 89%; P < 0.00001) in this comparison. Figure 3 demonstrates no significant difference between PRP Injection and oxygen-zone therapy groups regarding VAS scores.

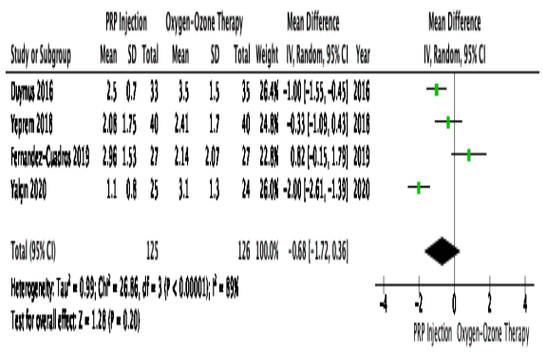

Figure 3 Forest plot for Visual Analog Scale (VAS) in knee osteoarthritis patients treated with PRP injection vs. Oxygen-Ozone therapy group.

The first-month mean difference in WOMAC pain scores between patients who received PRP injections and those who received oxygen-ozone therapy amounted to -1.14 points, yet it proved non-significant (MD: -1.14; 95% CI: -5.08, 2.79; P = 0.57) with substantial heterogeneity (I2 = 95%; P < 0.00001). The analysis revealed no significant difference between pain scores from PRP injection compared to oxygen-ozone therapy patients, as Figure 4 demonstrates.

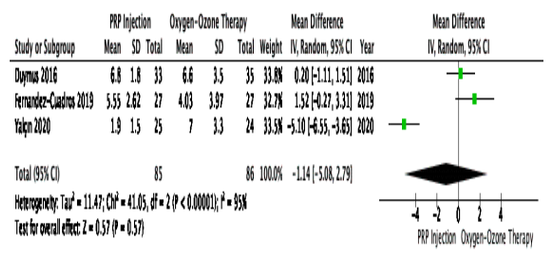

Figure 4 Forest plot for Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for Pain in knee osteoarthritis patients treated with PRP injection vs. Oxygen-Ozone therapy group.

There was a significant difference in WOMAC Stiffness scores between PRP injection and oxygen-ozone therapy at one-month follow-up, which amounted to -0.30 points (MD: -0.30; 95% CI: -0.54, 0.06; P = 0.02) with low heterogeneity (I2 = 25%; P = 0.26). Tests revealed a substantial difference in stiffness levels between subjects receiving PRP Injections versus oxygen-zone therapy treatment, according to Figure 5.

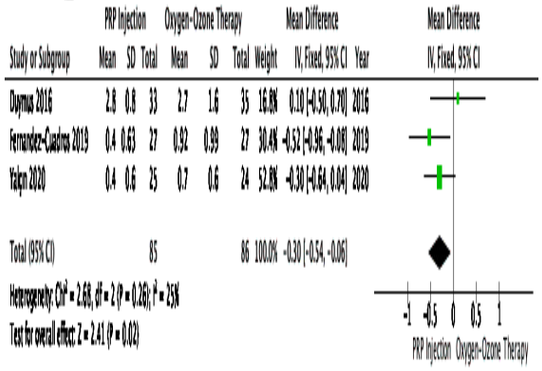

Figure 5 Forest plot for WOMAC for Stiffness in knee osteoarthritis patients treated with PRP injection vs. Oxygen-Ozone therapy group.

The first-month assessment revealed a significant difference measured by Function score where the Platelet-Rich Plasma Injection group achieved -2.95 points lower than the Oxygen-Ozone Therapy group (MD: -2.95; 95% CI: -5.25, 0.65; P = 0.01) with no heterogeneity (I2 = 0%; P = 0.60). The Function scores demonstrated a statistically significant difference between patients who received PRP Injection and those in the oxygen-ozone therapy group, as shown in Figure 6.

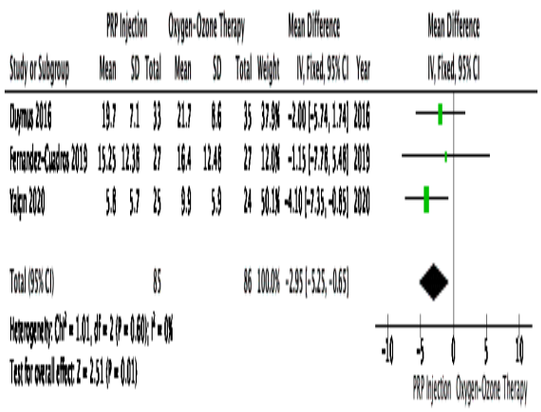

Figure 6 Forest plot for WOMAC for Function in knee osteoarthritis patients treated with PRP injection vs. Oxygen-Ozone therapy group.

DISCUSSION

The evaluation of PRP injection effectiveness compared with oxygen-ozone therapy used data from four RCTs with 251 participants suffering from KOA. Studies demonstrate that PRP injection achieves better pain relief and functional results when compared to oxygen-ozone therapy because both the VAS and WOMAC scores showed lower values in the majority of investigations. Additional investigations must proceed to validate these findings due to inconsistent study results. This latest review of grouped studies found that VAS results demonstrated no substantial change between PRP injection applications or oxygen-ozone therapy methods. The research by Duymus et al. (2016) showed that patients experienced better pain relief with PRP injections as the mean VAS score reached 2.5 ± 0.7 versus 3.5 ± 1.5 in oxygen-ozone therapy group.(Duymus et al., 2017)

The VAS scores from Yalçın (2020) indicated PRP injection recorded 1.1 ± 0.8 as opposed to oxygen-ozone therapy's 3.1 ± 1.3 score that confirmed PRP's potential superiority for pain relief.[14] The research agrees with studies showing that PRP, with its growth factor and cytokine content, enhances tissue repair and inflammatory response on a superior level versus oxygen-ozone therapy. Most studies demonstrate that PRP injection outperforms pain, stiffness, and functional assessment metrics according to the WOMAC scale. Patients receiving PRP treatment showed decreased WOMAC scores for pain, stiffness and functional ability, according to Duymus et al. (2016).(Duymus et al., 2017) Yalçın (2020) reported that patients treated with PRP injections obtained better knee function by demonstrating reduced WOMAC scores in every domain.(Yalçın, 2020) The research indicates that PRP injections deliver pain relief while simultaneously enhancing joint function and stiffness reduction, leading to superior life quality enhancements for knee OA patients. The research conducted by Fernandez-Cuadros et al. (2019) generated different findings because oxygen-ozone therapy induced a VAS mean score (2.14 ± 2.07) that proved lower than PRP injection's outcome (2.96 ± 1.53).(Fernandez-Cuadros et al., 2019)

The variance in study, patient data, and treatment methods could explain the different results observed in these studies. Two major variables can affect the results: the amount of ozone utilized and the number of PRP injections received during treatment. The variability between patient study groups, including baseline disease severity differences or comorbidities, possibly affects the outcomes. Visual analyses of VAS and WOMAC scores show varied study results in the available research reports. Research findings that support PRP injection as superior still show overlaps in confidence intervals with other studies, thus suggesting that their specific treatment effects cannot always be proven statistically significant.

The evaluation requires scrutiny of study particularities together with possible bias factors during interpretation. This meta-analysis has several limitations. The conclusions may not apply broadly because the study included only four RCTs which worked with total samples of 251 participants. The VAS and WOMAC pain outcomes showed substantial heterogeneity ($I^2 > 75\%$) which suggests procedural variations between studies that could influence the study results. A 1-month brief follow-up period in the current research prevents scientists from evaluating long-term therapeutic success. The research encountered methodological biases because PRP preparation methods and ozone dosage levels showed inconsistencies. A selection bias appears in the research because non-English studies are not included. The future development of studies should implement longer-lasting multi-site randomized controlled trials using standardized approaches.

CONCLUSION

This meta-analysis shows that KOA patients might achieve better pain relief together with improved function outcomes from PRP injections than oxygen-ozone therapy based on joint stiffness and functionality WOMAC scores. The clinical data indicates that PRP shows better treatment results for KOA. Additional randomized controlled trials, which directly compare PRP to oxygen-ozone therapy, should be conducted to substantiate existing evidence because studies show variable outcomes as well as critical methodology issues.

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