



Intra-articular ozone therapy efficiently attenuates pain in knee osteoarthritic subjects: A systematic review and meta-analysis

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ABSTRACT

Objectives: Ozone (O₃) gas is being used for chronic pain relief in knee osteoarthritis (KOA). However, there are controversies whether this gas can be medically useful in KOA pain treatments. The aim of this study was to evaluate the effectiveness of intra-articular ozone therapy for pain relief in KOA subjects using a systematic review and meta-analysis and standardized mean difference (SMD) as the effect size.

Method: Using specialized biomedical online databases of Pubmed Central, Pubmed, Medline, Google scholar, Scopus and Embase databases without the beginning date restriction until July 2018, the systematic review retrieved 10 studies for meta-analysis after fulfilling the inclusion and exclusion criteria.

Results: Analysis of Q and I²% indices showed a high heterogeneity in the selected studies (2600.330 and 99.654, respectively), thus, the random-effects model was chosen for SMD calculation. The primary analysis for the main hypothesis found that the weighted pooled effect size for the impact of intra-articular ozone therapy for pain reduction was as follows: SMD = −28.551 (95% confidence interval, −32.553 to −24.549). The P-value for the significance of the combined SMD examined by the z-test was 0.000 and thus, it was clearly considered statistically significant.

Conclusion: This meta-analysis presents evidence that intra-articular ozone therapy is an effective way for chronic pain management in KOA.

1. Introduction

Acute pain is a neuronal sensation that alerts a tissue injury, whereas chronic pain commonly defined as any pain, which lasts more than 12 weeks. One of the diseases with chronic pain comorbidity is osteoarthritis. The typical joints involved with osteoarthritis include hip and knee, as well as hands, feet, and spine. Osteoarthritis-induced loss of joint function plays a pivotal role in work disability and reduced quality of life in affected individuals. Although osteoarthritis eventually affects all joints of the body, it begins with progressive articular hyaline cartilage structure degradation and loss of function (chondropenia), typically in a focal manner.¹ As chondropenia progresses further damaging and eroding of cartilage occurs causing full-thickness cartilage loss over time and abnormal remodeling of the sub-articular bone, typically accompanied by the growth of osteophytes. Laxity of ligaments, weakness of periarticular muscles and synovitis may follow, eventually leading to malalignment due to joint tilting. Malalignment accelerates

joint structural deterioration by increasing local loading forces and acts as a risk factor for joint failure. KOA is a common disabling and degenerative articular disease leads to decrease in body function due to painful joints and knee articular stiffness.² The unsuccessful treatment of KOA, unfortunately, leads to partial or total knee replacement surgeries over time. One of the chronic pain treatment candidates is intra-articular ozone therapy. Thus, ozone may be a probable analgesic molecule. Ozone gas is a dynamically unstable structure molecule consisting of three oxygen atoms. For the past few years, the therapy of several musculoskeletal disorders with ozone has raised concern gradually. However, judicious application of ozone therapy in chronic pain management has yielded striking results and there are controversies whether this gas can be medically useful in KOA treatments.³ Thus, in the present study, we aimed to assess the effectiveness of intra-articular ozone therapy for pain relief in KOA subjects using a systematic review and meta-analysis under random-effects model and SMD as the effect size.

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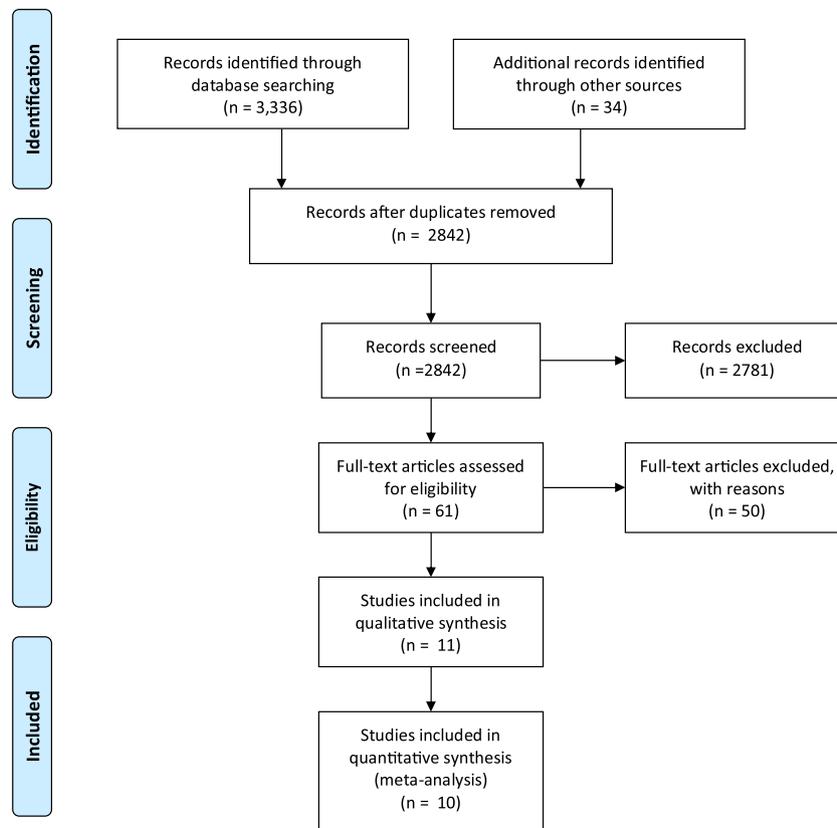


Fig. 1. Searching strategy in the systematic review. The flowchart illustrates the process of identifying relevant studies to be included into the investigation according to the accepted exclusion and inclusion criteria for intra-articular ozone therapy in knee osteoarthritic subjects.

2. Methods

2.1. Protocol of the systematic review and meta-analysis

The PRISMA Checklist 2009 was used to conduct this systematic review and meta-analysis.⁴

2.2. Information sources and search strategies

A systematic literature search was independently carried out by five authors (A. N., S. B., R. K., K. H., and S. D.) using specialized biomedical online databases of Pubmed Central, Pubmed, Medline, Google scholar, Scopus and Embase databases without the beginning date restriction until July 2018. Publications using the non-MeSH and MeSH terms “osteoarthritis”, “pain” in combination with “ozone” with additional keywords such as “knee”, “intra-articular” and “therapy” were identified.

2.3. Eligibility criteria

Studies were pre-included if they used standardized methods such as visual analogue scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for pain assessments in the osteoarthritic patients before and after the therapy. No limitation was applied to the severity of osteoarthritis, type of pain scale, race, gender, and age of the study participant subjects. However, studies were excluded if they enrolled populations other than knee osteoarthritis as well as reports describing non-ozone interventional therapies. We only considered ozone therapies for the effect size analyses in each study in the pre- and post-therapy results.

2.4. Study selection

Only studies providing enough information about their results such as pain levels, number of cases, standard deviation (SD), or standard error of the mean (SEM), etc., in such a way to compute an estimate of the effect size for pain before and after ozone therapy in the osteoarthritic subjects were included. Due to the different protocol definition used for pain levels assessment, only studies, which determined pain levels according to VAS and WOMAC criteria in osteoarthritic cases, were selected.

2.5. Data collection process

The first author of the selected paper, publication year, the levels of pain, in osteoarthritis subjects, evaluated criteria for the pain and the total number of cases and other related information were extracted from the selected publications which have been provided by the systematic review process for using in the meta-analysis.

2.6. Summary measures and synthesis of results

Stata version 14.0 (Stata Corporation, College Station, TX, USA) was employed for data meta-analysis. Between-study heterogeneity was assessed using the χ^2 based Q-test and I^2 as well. The Q test and I^2 statistics were applied to evaluate the heterogeneities among the selected studies. A significant Q suggests the existence of heterogeneities among the studies and also I^2 estimates the magnitude of these inconsistencies.⁵ In the current study, the random-effects model of meta-analysis and SMD (for calculation of estimated pooled effect size) were applied. The SMDs have been presented with 95% confidence interval for all studies and the combined effect. The significance of each calculated SMD was examined by the z-test and $P < 0.05$ considered

Table 1
The demographic data provided from the selected studies after the systematic review process.

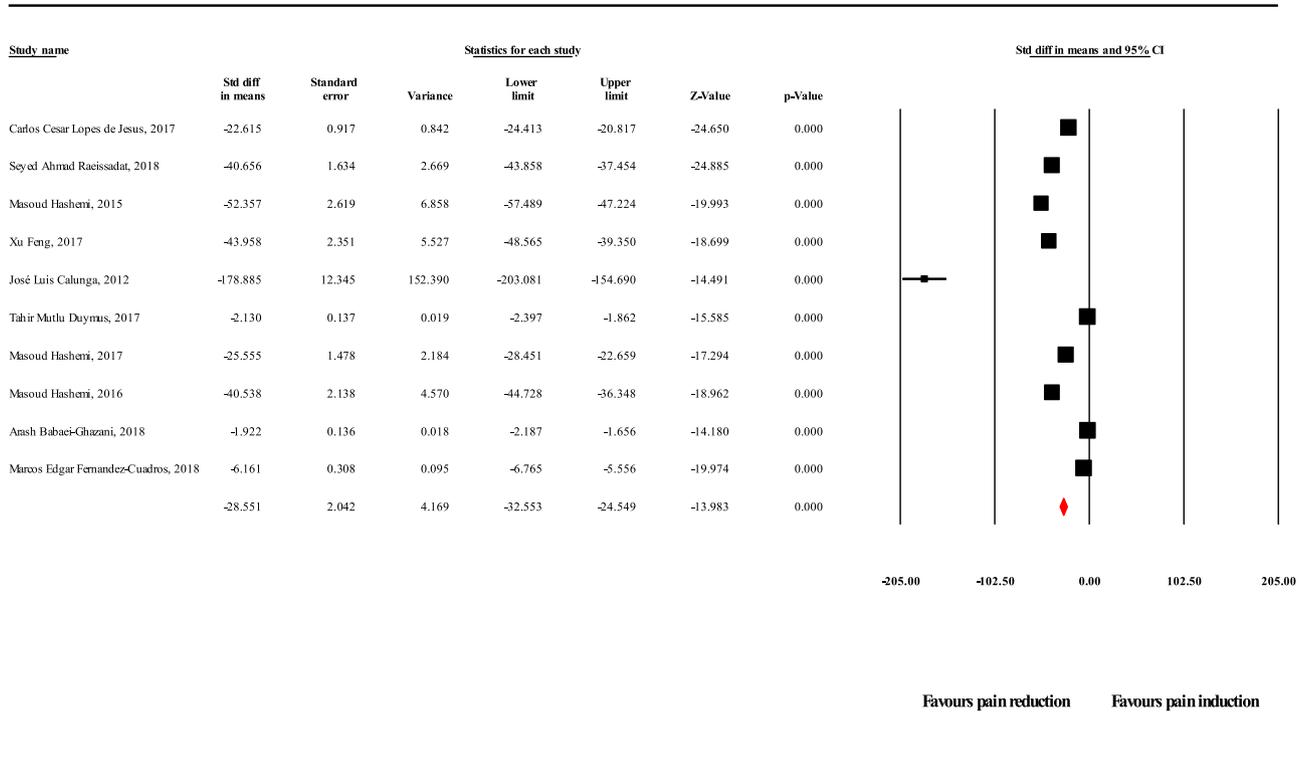
Reference number	Study	Article Title	Country	Number of cases	Age range	WOMAC before ozone therapy (mean ± SD)	WOMAC after ozone therapy (mean ± SD)	10 cm VAS before ozone therapy (mean ± SD)	10 cm VAS after ozone therapy (mean ± SD)	Time of pain evaluation (after injection)	Dose of injection: volume (concentration) as described by the authors	Criteria for knee osteoarthritis as reported by the authors
1	Carlos CeÁsar Lopes de Jesus, 2017	Comparison between intra-articular ozone and placebo in the treatment of knee osteoarthritis: A randomized, double-blinded, placebo-controlled study	Brazil	61 Female = 56 Male = 5	60-85	60.0	20.0	7 ± 4.37	0 ± 4.37	8 weeks	10 ml (20 µg/ml), once a week, for 8 consecutive weeks	Criteria of the American College of Rheumatology and Kellgren Lawrence grades II-III
2	Seyed Ahmad Raeesadat, 2018	Intra-articular ozone or hyaluronic acid injection: Which one is superior in patients with knee osteoarthritis? A 6-month randomized clinical trial	Iran	67 Female = 50 Male = 18	45-75	40.8 ± 9.0	20.4 ± 5.0	7.6 ± 2.8	2.6 ± 2.0	6 months	10 ml (30 µg/ml), 3 weekly injections	Kellgren–Lawrence radiologic grades II-III
3	Masoud Hashemi, 2015	The Effects of Prolotherapy With Hypertonic Dextrose (Ozone) in Patients With Knee Osteoarthritis	Iran	40 Female = 23 Male = 17	40-75	56.3 ± 11.5	81.6 ± 13.7	7.6 ± 1.3	2.8 ± 1.1	3 months	5-7 ml (15 g/ml), injections were repeated three times with 7–10 days interval for each patient	Kellgren-Lawrence grades I and II
4	Xu Feng, 2017	Efficacy of Ozone Injection into the Knee for the Osteoarthritis Patient along with Oral Celecoxib and Glucosamine	China	35 Female = 20 Male = 15	50-78	not provided by the authors	not provided by the authors	7.89 ± 1.08	3.46 ± 1.04	6 weeks	20 ml (20 µg/ml), for six weeks, twice a week for each patient	Chinese medical association of rheumatology and Kellgren-Lawrence Grades lower than III and IV
5	José Luis Calunga, 2012	Application of Ozone Therapy in Patients with Knee Osteoarthritis	Cuba	42 Female = not provided by the authors Male = not provided by the authors	45-65	not provided by the authors	not provided by the authors	9 ± 0.02	1 ± 0.02	1 month	Ozone was administered by rectal way (20 sessions, daily, Monday to Friday) at scaling doses, using ozone concentrations between 25 and 40 mg/l and volumes of 100 to 200 ml and by intra-articular (twice per week) applications with an ozone concentration of	Not mentioning a specific criteria: radiologically diagnosed as patients with knee osteoarthritis

(continued on next page)

Table 1 (continued)

Reference number	Study	Article Title	Country	Number of cases	Age range	WOMAC before ozone therapy (mean ± SD)	WOMAC after ozone therapy (mean ± SD)	10 cm VAS before ozone therapy (mean ± SD)	10 cm VAS after ozone therapy (mean ± SD)	Time of pain evaluation (after injection)	Dose of injection: volume (concentration) as described by the authors	Criteria for knee osteoarthritis as reported by the authors
6	Tahir Mutlu Duymus, 2017	Choice of intra-articular injection in treatment of knee osteoarthritis: platelet-rich plasma, hyaluronic acid or ozone options	Turkey	35 Female = 31 Male = 4	> 50	31.1 ± 12.9	76.6 ± 10.7	3.5 ± 1.5	7.3 ± 1.03	6 months	20 mg/l and volumes between 5 and 10 ml 15 ml (30 µg/ml), four doses	Kellgren–Lawrence Grade 2 or 3
7	Masoud Hashemi, 2017	Effect of intraarticular injection of ozone on inflammatory cytokines in knee osteoarthritis	Iran	30 Female = 19 Male = 11	35-75	not provided by the authors	not provided by the authors	6.8 ± 1.7	2.2 ± 1.5	6 months	5 ml (35 µg/ml), not provided by the authors explicitly	Not mentioning a specific criteria: The inclusion criteria were patients with chronic osteoarthritis aged between 35 to 75 years and knee osteoarthritis.
8	Masoud Hashemi, 2016	The Comparison between Two Methods for the Relief of Knee Osteoarthritis Pain: Radiofrequency and Intra-Periarticular Ozone Injection: A Clinical Trial Study	Iran	36	30-80	not provided by the authors	Not provided by the authors	9 ± 1.43	1.43	12 weeks	intra articular ozone injection (10 ml O2-O3 mixture 40 µg/ml) and periarticular injection (5 ml O2-O3 mixture 10µ g/ml). This procedure was performed three times during the first week and twice during the second week and once in every next three weeks.	Kellgren–Lawrence Grade 2 or 3
9	Arash Babaei-Ghazani, 2018	The effects of ultrasound guided corticosteroid injection compared to oxygen–ozone (O2–O3) injection in patients with knee osteoarthritis: a randomized controlled trial	Iran	31 Female = 24 Male = 7	40-75	6.261 ± 2.0871	4.781 ± 2.0186	7.735 ± 1.6382	5.316 ± 2.6771	3 months	10 ml (15 µg/ml) of oxygen–ozone	American College of Rheumatology criteria; (2) grades I, II (mild), and III (moderate) consistent with the Kallgren-Lawrence radiologic criteria; (3) knee pain for at least the last 6 months; and (4) 40–75 years of age
10	Marcos Edgar Fernandez-Cuadros, 2018	Intra Articular Ozone Reduces Serum Uric Acid and Improves Pain, Function and Quality of Life in Knee Osteoarthritis Patients: A Before-and-After Study	Spain	42 Female = 31 Male = 11	66.90 ± 8.83 (mean ± SD)	14.26 ± 2.61	5.95 ± 2.97	7.02 ± 1.20	2.97 ± 1.48	4 weeks	four sessions (one session/week) of an intra articular infiltration of a medical mixture of oxygen-ozone (95% - 5%), 20 ml volume at a 20 µg/ml concentration	Criteria of American College of rheumatology and on radiological signs, graded from 2 to 4 (based on Kellgren and Lawrence grading sys tem

Meta-analysis for intra-articular ozone therapy in knee osteoarthritis subjects



Random-effects model

Fig. 2. Forest plot of 10 included studies fulfilled the inclusion and exclusion criteria. In this presentation, pooled data evaluating the effect of intra-articular ozone therapy in knee osteoarthritis subjects has been demonstrated. This meta-analysis was performed under the random-effects model (Q test = 2600.330 and I² test = 99.654). The pooled point estimate standardized mean difference (SMD) was -28.551 (95% confidence interval, -32.553 to -24.549). The weighted SMD for individual studies represented by a square on the forest plot with 95% confidence interval around the mean point shown by a solid line.

statistically significant.

2.7. Risk of bias across studies

For the risk of bias across studies, the publications were scrutinized for method validation and data processing and for estimated effect size estimation from the selected studies; the funnel plot was developed as well. For interpreting any publication bias among studies, visual inspections of the generated funnel plot were employed to evaluate the asymmetry. In this plot, the Y and X axes represent the standard error and standardized difference in means, respectively. In addition, meta-regression of pain evaluation time against the standard difference in means was plotted under fixed-effect model. The Duval and Tweedie’s trim and fill results were prepared under both random- and fixed-effect models as well.⁶

3. Results

3.1. Study selection

The study selection flowchart in this systematic review has been presented in Fig. 1. The initial search for ozone therapy identified a total of 3370 potentially eligible studies and 528 records removed being as duplicates. Of the 2842 remaining records, 2781 publications were excluded after reading the titles or abstracts as being obviously

irrelevant to the goal of this meta-analysis. Moreover, because of insufficient data presented by the authors of such publications for calculation of the SMD and 95% CI and because of poor quality (such as either not reporting the mean and standard deviations for pre and post injections or the exact time course of pain evaluations in weeks or month), one paper was excluded which has been cited as reference number.^{6,7} The selection process of studies was independently done by five authors (A. N., S. B., R. K., K. H., and S. D.) and the disagreements were resolved by the first author. Finally, ten studies (which have been detailed in Table 1 and cited in the references part of the current study as 7–16^{8–17}); were included in the meta-analytical processes for intra-articular ozone therapy in KOA (Fig. 1).

3.2. Study characteristics

For each study, the epidemiologic and subject characteristics data, which have been reported by the authors, were extracted. The number of cases, pain definition criteria, mean age, etc., have been presented in Table 1. Actually, this meta-analysis retrieved a total number of 398 knee osteoarthritic cases until July 2018 for knee osteoarthritis.

3.3. Risk of bias within studies

The results showed that the selected studies were heterogeneous and actually, the Q test was 2600.330 for intra-articular ozone therapy

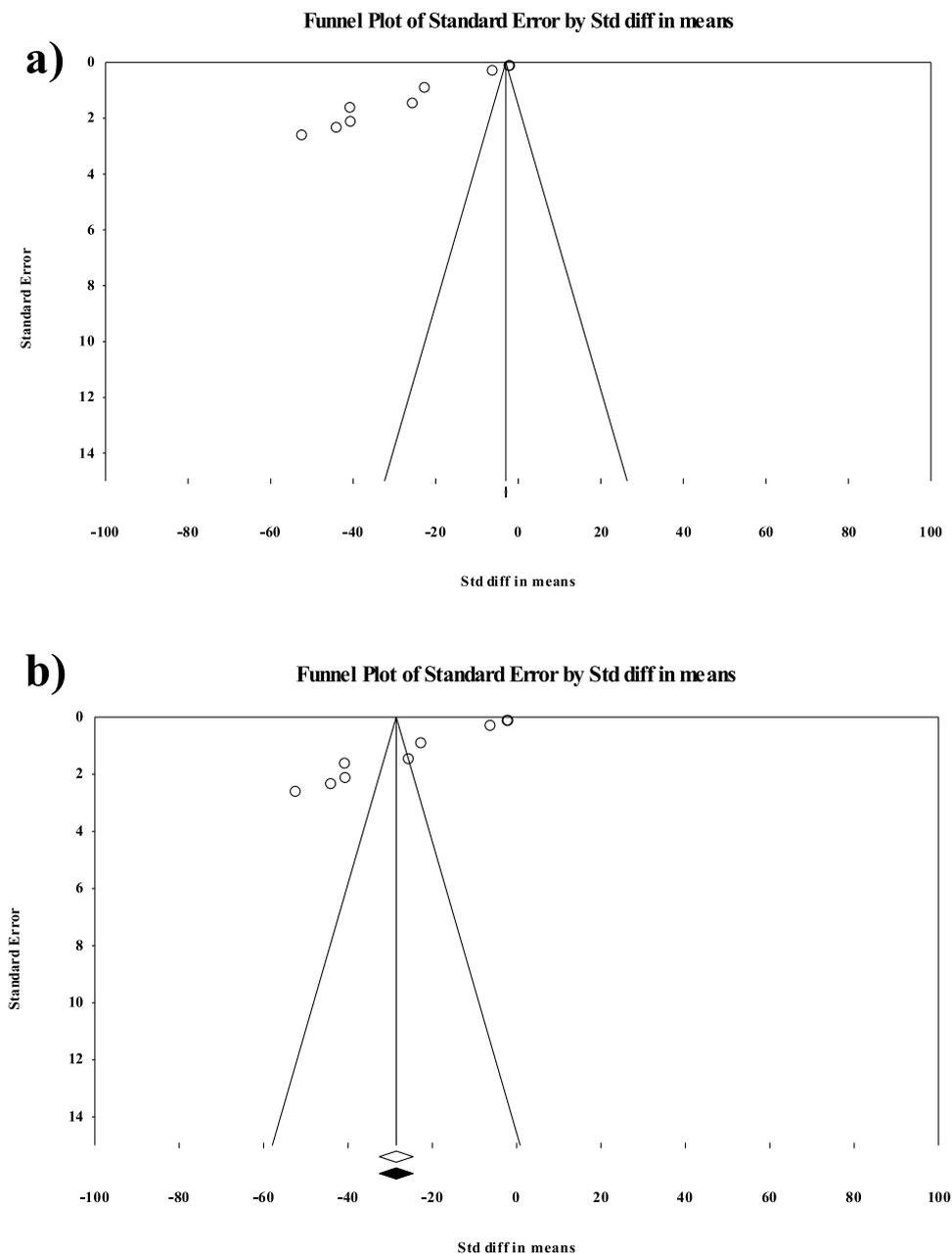


Fig. 3. Funnel plot of included studies. For interpretation of any publication bias among studies, visual inspection of the generated funnel plot was employed to evaluate symmetry. The funnel plot appears asymmetrical under fixed-effect model (a) and somewhat symmetrical under random-effects model (b) showing the effectiveness of intra-articular ozone therapy for chronic pain relief in knee osteoarthritic patients. In this plot, the Y and X axes represent the standard error and standard difference in means, respectively.

in the selected studies. The Q statistic test is only applied for testing the heterogeneity, but not suitable for calculation of the heterogeneity extent in the studies. However, it has been proposed a tentative classification of I^2 values with the purpose to interpret heterogeneity magnitude. Thus, the percentages around 25% ($I^2 = 25$), 50% ($I^2 = 50$), and 75% ($I^2 = 75$) would be mean low, medium, and high

heterogeneity, respectively.⁵ Moreover, the I^2 test was 99.654 for intra-articular ozone therapy in the subjects. As I^2 index and the between-studies variance, τ^2 , are directly related: the higher the τ^2 , the higher the I^2 index.⁵ Therefore, the random-effects model of meta-analysis was applied for forest plot presentation of the selected studies in ozone therapy in the subjects.

Regression of Time of pain evaluation (weeks after injection) on Std diff in means

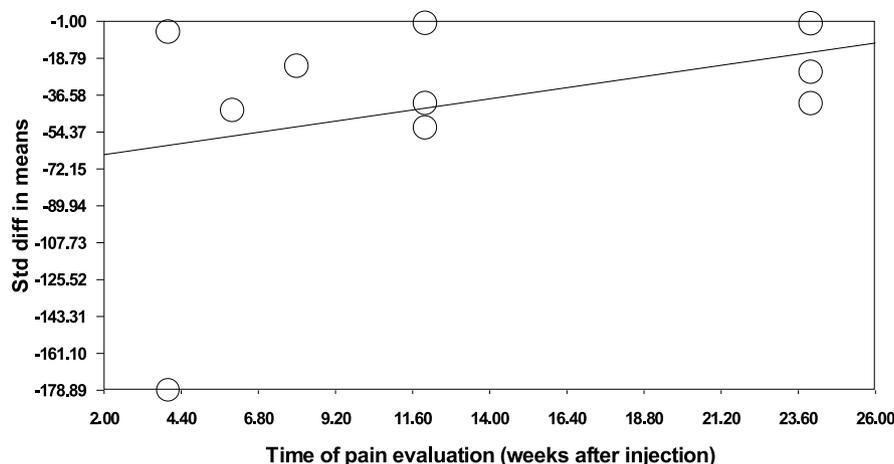


Fig. 4. Meta-regression results under fixed-effect model. Meta-regression of pain evaluation time against the standard difference in means was plotted. The results confirmed the heterogeneity of the results using included studies.

3.4. Synthesis of results

The forest plot showed the mean effect size and SD and the SMD with 95 percent of a CI for each study and the pooled effect size as well. The primary analysis for the main hypothesis found that the weighted average effect size for the impact of ozone therapy in pain reduction was as follows: SMD = -28.551 (95% confidence interval, -32.553 to -24.549) using the random-effects model in the meta-analysis as presented in Fig. 2 for the 10 included studies. The P-value for the significance of the combined SMD examined by the z-test for intra-articular ozone therapy was 0.000 and it was clearly considered statistically significant.

3.5. Risk of bias across studies

Moreover, the shape of the funnel plot considered asymmetrical under fixed-effect model (confirming publication bias) and somewhat symmetrical under random-effects model confirming positive effects of intra-articular ozone therapy as an analgesic gas in the recent reports related to in knee osteoarthritic subjects (Fig. 3). In addition, meta-regression under fixed-effect model confirmed the bias among the results of the studies as well (Fig. 4). The Duval and Tweedie's trim and fill results under both random- and fixed-effect models have been presented in Table 2.

4. Discussion

In the current study, we studied the effects of ozone therapy on KOA pain relief through a systematic review and meta-analysis of studies relating to intra-articular ozone injection in subjects. KOA imposes a heavy financial burden on the affected individuals and their families. Therefore, finding new efficacious therapies are of high interest. Epidemiological studies revealed that half of the world's population aged 65 years or older suffering from osteoarthritis, which is the most prevalent disorder of articulating joints in humans.¹⁸ Hence, discovering new efficient pain treatments is of top priority and indeed according to the recent survey, on average 54.4 million (22.7%) adults had doctor-diagnosed arthritis, and 23.7 million (43.5% of those with

arthritis) had arthritis-attributable activity limitations. It also reveals that the prevalence of arthritis is high, particularly among adults with comorbid conditions, such as obesity, diabetes, and heart disease. Furthermore, the prevalence of arthritis-attributable activity limitations is high and increasing over time.¹⁹ Osteoarthritis is defined as either primary or secondary to a diagnosed cause. Primary osteoarthritis is the most commonly diagnosed form of the disease and considered to occur largely due to "wear and tear" over time. On the other hand, secondary osteoarthritis results from conditions that induce a change in the microenvironment of the cartilage. Such conditions include significant trauma, congenital joint abnormalities, metabolic defects (e.g., Wilson disease), infections, diseases (e.g., neuropathic), and disorders that alter the normal structure and function of cartilage (e.g., rheumatoid arthritis, gout). The secondary form tends to appear in individuals aged approximately 45 or 50. In the selected studies, the type of KOA was not reported by the authors for sub-group analysis. However, the results showed that intra-articular ozone therapy alleviates pain suffering in the patients. Besides of anti-inflammation, this gas exerts its therapeutic effects through modulating a variety of pathways including accelerating glucose usage in cellular metabolism, improving protein metabolism, converting unsaturated fatty acids into hydrosoluble compounds, and increasing erythrocyte activity.²⁰ In this meta-analysis, after evaluations for inclusion and exclusion criteria, the 10 selected studies were heterogeneous and thus, random-effects model applied for further evaluation of ozone therapy in the patients. The heterogeneity may be attributed to factors such as the different ozone doses researcher used, time of period for evaluation of pain relief, gender differences, etc. Analysis for publication bias showed that all of the publication unequivocally reports the effectiveness of intra-articular ozone therapy in KOA and thus there is a positive bias in pain relief actions of ozone therapy in the publications. Moreover, the pooled SMD, as the calculated effect size was high, also emphasizing the ozone effectiveness therapy. As the non-operative and less invasive management of patients with KOA is of interest, ozone therapy may be in focus as a treatment option. Moreover, intra-articular ozone therapy may be used either in combination with another therapy or alone for knee osteoarthritic subjects and it might delay the partial or total replacement of the knee in patients suffering from primary or secondary osteoarthritis.

Table 2
The Duval and Tweedie's trim and fill results (look for missing studies to right of mean).

a) Under fixed-effects model		Fixed Effects				Random Effects				Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit
Observed values	5	-2.99662	-3.17473	-2.81851	-28.55093	-32.55305	-24.54881	-28.55093	-32.55305	-24.54881
Adjusted values		-2.67970	-2.85713	-2.50227	-6.08234	-10.27454	-1.89014	-6.08234	-10.27454	-1.89014
b) Under random-effects model		Fixed Effects				Random Effects				Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit
Observed values	0	-2.99662	-3.17473	-2.81851	-28.55093	-32.55305	-24.54881	-28.55093	-32.55305	-24.54881
Adjusted values		-2.99662	-3.17473	-2.81851	-28.55093	-32.55305	-24.54881	-28.55093	-32.55305	-24.54881

5. Conclusion

In conclusion, the results of the current study suggest that the use of intra-articular injection of ozone gas may be an effective way to relieve disease-associated chronic pain.

Declaration of conflicting interests

The authors have no conflicts of interest.

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