Ozone for the treatment of temporomandibular joint disorders: a systematic review and meta-analysis

Rafael Torres-Rosas[1], María Eugenia Marcela Castro-Gutiérrez[2], Luis Angel Flores-Mejía[3], Eduardo Ulises Torres-Rosas[4], Roberto Miguel Nieto-García[5], Liliana Argueta-Figueroa[6, 7, *]

1 Laboratorio de Medicina Complementaria, Centro de Estudios en Ciencias de la Salud y la Enfermedad, Facultad de Odontología, Universidad Autónoma "Benito Juárez" de Oaxaca, Oaxaca, México
2 Programa de Doctorado en Biociencias, Facultad de Medicina y Cirugía, Universidad Autónoma "Benito Juárez" de Oaxaca, Oaxaca, México
3 School of Public Health, Imperial College London, London, UK
4 Facultad de Derecho, Universidad Autónoma Nacional de México, Cuidad de México, México
5 Centro Interdisciplinario de Investigación para el Desarrollo Integral Regional (CIIDIR), Unidad Oaxaca, Instituto Politécnico Nacional, Oaxaca, México
6 Cátedras CONACyT – Facultad de Odontología, Universidad Autónoma "Benito Juárez" de Oaxaca, Oaxaca, México
7 Laboratorio de Biomateriales, Centro de Estudios en Ciencias de la Salud y la Enfermedad, Facultad de Odontología, Universidad Autónoma "Benito Juárez" de Oaxaca, Oaxaca, México

*Correspondence to: Liliana Argueta-Figueroa, DDS, MDSc, PhD, l_argueta_figueroa@hotmail.com, or liliana.argueta@conacyt.mx.
orcid: 0000-0002-1044-6757 (Liliana Argueta-Figueroa)

Abstract

Temporomandibular joint disorders (TMD) generate pain and difficulties for mouth opening affecting the patients' quality of life. Ozone is an emerging therapy that has been proposed as a potential treatment, due to that, the evidence about its efficacy should be reviewed. Therefore, this work aimed to conduct a comprehensive systematic review to address the efficacy of ozone therapy for the treatment of pain and limited mouth opening in patients with TMD. The design of the included studies was clinical trials and observational studies, whereas, a series of cases, in vivo, and in vitro studies were excluded. The search was performed in PubMed, ClinicalTrials, Web of Science, and Scopus. Gray literature was searched at Google Scholar. Relevant data of all included studies were recorded. The risk of bias (using RoB 2) and the quality (using Grading of Recommendations Assessment, Development, and Evaluation) assessments were carried out. Meta-analyses using random-effects models of pain and maximal mouth opening data were performed. This review included 8 studies with 404 participants suffering limited function and pain related to TMD. At the overall bias of the studies, 25% exhibited some concerns and 75% had high risk; and the quality of the studies was low. The analysis of the included studies suggests that ozone therapy can diminish pain and improve the maximal mouth opening in TMD patients. However, there is no conclusive evidence of ozone therapy as a superior treatment for TMD compared with occlusal splint and pharmacotherapy.

Key words: bio-oxidative therapy; evidence-based medicine; mouth opening; oral rehabilitation; ozone therapy; pain; qualitative analysis; temporomandibular joint

doi: 10.4103/2045-9912.345174
How to cite this article: Torres-Rosas R, Castro-Gutiérrez MEM, Flores-Mejía LA, Torres-Rosas EU, Nieto-García RM, Argueta-Figueroa L. Ozone for the treatment of temporomandibular joint disorders: a systematic review and meta-analysis. Med Gas Res. 2023;13(3):149-154.
Funding: The work was supported by the National Council on Science and Technology (CONACyT), No. 755117 (to MEMCG).

Introduction

The temporomandibular joint (TMJ), jaws, muscles, ligaments, periodontium, and dental organs constitute a harmonic functional stomatognathic unit. Any alteration on its components can result in homeostatic rupture known as TMJ disorders (TMD) with a set of signs and symptoms.[1,2] The American Dental Association includes TMD a heterogeneous group of clinical conditions that are characterized by pain and dysfunction of the masticatory system. The International Consortium Network established a model for pain research: the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD). That tool was replaced in 2014 by the DC/TMD for both clinical and research use.

In an epidemiological study, with volunteers aged 18 to 44 years, it was found that every year 4% of the subjects developed a harmonic and functional stomatognathic system and the prevalence of painful TMD was high considering that 6 months later, 49% of incident cases exhibited TMD.[3] The most common TMD symptoms are articular crepitus, asymmetric mandibular movements, limited mouth opening, and facial muscle pain. This disorder can evolve to chronicity if proper treatment is not provided. TMD may negatively influence social and work relationships, and in consequence, decrease quality of life.[4]

TMD is frequent and even 1 of 10 patients with TMD suffers severe pain-related disability,[5] which directly affects their quality of life.[6] It has been reported that in TMD, there is an increased risk of presenting a greater number of painful sites as well as coexisting pain and comorbidities when the duration of pain in TMD is prolonged.[7] This persisting pain is probably attributable to the central sensitization mechanism, which is time-dependent. The disorder can evolve to chronicity if proper treatment is not provided. Hence, the importance of avoiding chronic pain, treating it in time with an effective therapy.[8] In that sense, the treatment of TMD is complex and requires a complete pharmacological scheme that includes anxiolytics, analgesics, muscle relaxants, and in some cases, even anti-depressants.[9] However, these treatments frequently have considerable adverse effects, making non-pharmacological

and complementary approaches potentially advisable options for pain treatment.[10]

In daily clinical practice, the patients with TMD mainly request that the therapy helps to restore their masticatory capacity, as well as being able to chew without pain. Today, several potential intervention strategies have been tried as therapy for TDM,[11] however, an ideal strategy should be able to change harmful dynamics linked to prolonged disorders. Ozone gas was discovered in the 19th century. After years of research, this gas has been applied to the medical field, being an innovative treatment, which is known as ozone therapy (OT). The medical community has recently pointed out that OT could be helpful in the treatment of infectious diseases such as dental caries, to control blood cholesterol, to improve lumbar discectomy,[12] to augment immune and anti-oxidative responses, also in the complementary treatment of the hypoxic and ischemic syndromes.[13]

The practitioners must be choosing the best evidence-based medicine therapy and cost-effective for providing long-term pain relief for TDM. Therefore, we performed a comprehensive systematic review of clinical trials and observational studies to address the efficacy of OT in comparison with conventional treatment for pain relief (assessed using Visual Analog Scale (VAS)) and limited mouth opening (measured in mm) in patients with TDM.

Data and Methods

Protocol registry

We conducted this systematic review according to the protocol registered in PROSPERO with the identification No. CRD42021242705 (Registration date: May 14, 2021).

Study design

The design of the studies included in the systematic review was randomized controlled trials, non-randomized clinical trials, cohorts and case-control studies. On the contrary, the studies excluded were case reports, case series, letters, comments, short communications, pilot studies, animal studies, *in vitro* studies, and literature reviews.

Eligibility criteria and participant characteristics of studies

The eligibility criteria were defined considering the PICO (Population, Intervention, Comparison, and Outcome) (**Table 1**).

Search strategy and databases used

The algorithms used for the search strategy and the electronic databases used are shown in **Table 1**. The search for grey literature was carried out on Scholar Google. The manual search was achieved through bibliographical references of the included studies in the review.

Study selection

The eligibility of the studies that could be included in the review was determined by reading the title and summary of each record identified at the search. Then the full-text of the selected articles that met the eligibility criteria were retrieved and reviewed in-depth. If reviewing the full-text, the studies that did not fully meet the eligibility criteria were excluded.

Data collection process and data items

A standardized Microsoft Excel worksheet was prepared for the registration of the relevant data of all included studies in the systematic review such as participant demographics and baseline characteristics; methodology; numbers of sessions and frequency; time intervals in which the effect of the intervention was measured; pain level score (the mean and standard deviation of Visual Analog Scale); maximal mouth opening (MMO); and Clinical Dysfunction Index at baseline and follow-ups. Two reviewers (MEMGC and EDTR) were responsible for data extraction, one reviewer extracted data, and the other revised the extracted data. The disagreements were discussed with all reviewers until reaching a consensus. The study researchers were contacted via email for missing data or additional details.

Risk of bias in individual studies and quality assessment

For assessment of the risk of bias of the included studies in the review, the recommendations from the Cochrane Handbook for Systematic Reviews of Interventions Chapter 814 and Risk of Bias 2 (RoB 2) tool were used for the assessment of the risk of bias.[15] Besides, we evaluated the quality of each study using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria.

Meta-analyses

The information collected from the selected studies was carefully analyzed to determine whether the studies can be grouped for each outcome (pain and MMO) and subgroups were performed using similar types of OT (transdermal and arthrocentesis) at the same time intervals of follow-up. Standardized mean difference was calculated for each study selected and then the data were combined using a random-effects meta-analysis. Besides, 95% confidence intervals and two-sided values were calculated. The heterogeneity among the studies, in terms of measures of effect, was evaluated using the I^2 statistic. An I^2 value greater than 50% was considered substantial heterogeneity.

Results

After searching, it was found a total of 95 records. After removing duplicates, 74 records remained and these were revised by title and abstract. Then, 10 full-text articles were retrieved, 2 of which were excluded with reasons. Eight articles[16–23] reported the use of OT for the treatment of TMD and the data extracted from these studies are listed in **Additional Table 1**. No gray literature matched the eligibility criteria. The study selection process is detailed in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram (**Figure 1**). In the overall bias of the included studies, 25% exhibited some concerns and 75% had high risk; the main problems in the randomized controlled trials were reporting and selection bias. The risk of bias for individual studies is shown in **Figure 2**. Also, the certainty of the evidence was low due to risk of bias, inconsistency and imprecision as shown in **Table 2**.

Table 1: Eligibility criteria according to PICO strategy and keywords used for the search

Item	Information
Population	The population of included studies must be patients with temporomandibular joint disorders (TMD) without other concomitant pathology that preferably were diagnosed using the diagnostic algorithms of Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD): recommendations from the International RDC/TMD Consortium Network workshop were included. In contrast, the patients with orthodontics treatment, patients with previous surgical treatment for TMD, patients with facial trauma history, coronoid hyperplasia, autoimmune diseases, and headache attributed to TMD, oral movement disorders, neoplasms, congenital/developmental disorders of the temporomandibular joint, osteonecrosis, synovial chondromatosis, or degenerative joint diseases, were excluded.
Intervention	The included studies preferably should use ozone therapy as an intervention for TMD treatment (transdermal ozone therapy (OT), injection of ozonized water).
Comparator	The included studies must use occlusal splint, pharmacotherapy, arthrocentesis or placebo as the control group.
Outcomes	The included studies must evaluate at least one of the following outcomes: 1) pain relief of TMD defined as a change in pain level score attributable to the intervention (before described) from a baseline to the available follow-ups assessed by the Visual Analog Scale (VAS), 2) the maximal mouth opening (MMO) defined as a change in the measurement of the maximal distance between the cutting edge of the maxillary and mandibular central incisors, 3) the clinical dysfunction index (CDI): the evaluation of Fricton's Craniomandibular Index (CMI), or Helkimo's Clinical Dysfunction Index (HCDI) or Fonseca Anamnestic Index (FAI).
Electronic database	Medline/PubMed, Clinical Trails.gov, Web of Science, Scopus, and Scholar Google
Focused question	Is the ozone an effective therapy for symptoms relief in patients with temporomandibular disorders?
Database: number of registries	Algorithms and keywords used
PubMed: *n*=7	("temporomandibular joint disorders" OR "temporomandibular disorders" OR "temporomandibular joint dysfunction syndrome") AND ("ozone" OR "ozonetherapy" OR "ozone therapy")
ClinicalTrials: *n*=0	Completed Studies | Studies With Results | Interventional Studies | Temporomandibular joint dysfunction syndrome | ozone OR "ozonetherapy" OR "ozone therapy"
Web of Science: *n*=4	# 2 TS= ("ozone" OR "ozonetherapy" OR "ozone therapy") # 1 TS= ("temporomandibular joint disorders" OR "temporomandibular disorders" OR "temporomandibular joint dysfunction syndrome") (Article) Index=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH
Scopus: *n*=13	TITLE-ABS-KEY (("temporomandibular joint disorders" OR "temporomandibular disorders" OR "temporomandibular joint dysfunction syndrome") AND ("ozone" OR "ozonetherapy" OR "ozone therapy"))
Scholar Google: *n*=71	("temporomandibular joint disorders" OR "temporomandibular disorders" OR "temporomandibular joint dysfunction syndrome") AND ("ozone" OR "ozonetherapy" OR "ozone therapy") AND ("placebo" OR "occlusal splints" OR "sham")

Note: PICO: Population, Intervention, Comparison, and Outcome.

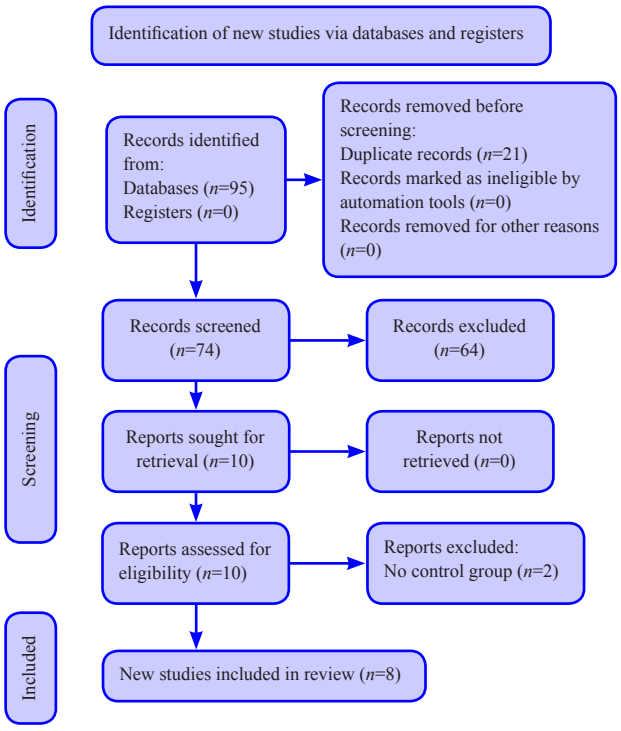

Figure 1: Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram of the selection process of the included studies in the systematic review.

Ozone treatments

Four studies evaluated the efficacy of high-frequency, bio-oxidative transdermal OT in patients with TMD. The sessions lasted 10 minutes once, 6 times per 2 weeks. Doğan et al.[16] and Yamaner et al.[17] applied ozone at 30% of concentration. Differently, Celakil et al.[18,19] performed two studies using an ozone concentration of 60%. On the other hand, three studies evaluated the efficacy of the ozone application in arthrocentesis of the TMJ with intraarticular disorder. The patients received 2 mL of ozonized water with 70 µg/mL.[20-22] Finally, Daif[23] injected 2 mL of ozone gas concentration at 10 µg/mL into the articular fossa of the TMJ. The injections were repeated twice per week for 3 weeks.

Pain outcomes

Concerning transdermal OT, Doğan et al.[16] evaluated pain perception changes by VAS in patients with painful TMD. The control group with pharmacological therapy receives ketoprofen and thiocolchicoside twice a day for 7 days. Their team reported improvement of pain in favor of OT after 2 weeks of treatment. Also, Celakil et al.[18] evaluated subjective pain levels with VAS diagnosis of myofascial pain dysfunction syndrome. The control group received sham OT, in the same number of sessions with de ozone device switched on but not programmed. The research team reported improvement in pain after 2 weeks of OT treatment. Two years later, Celakil

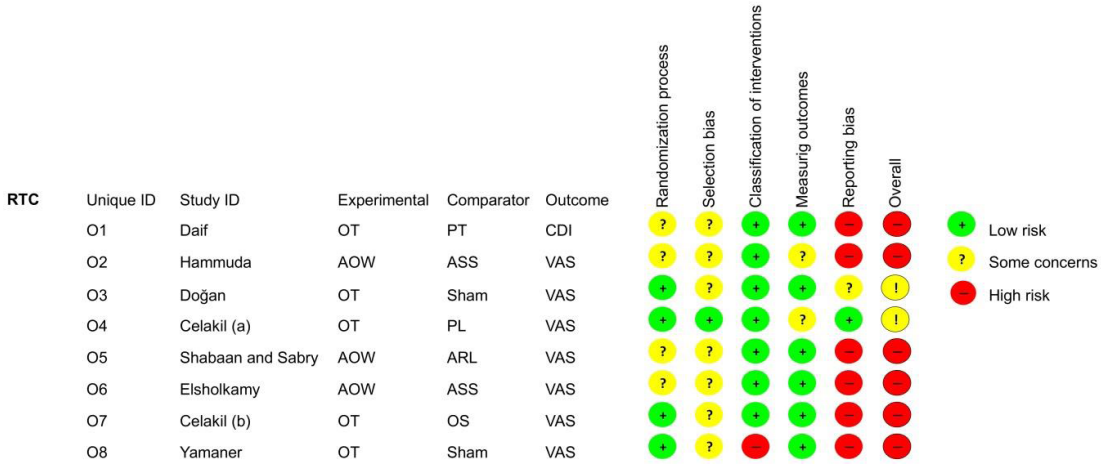

Figure 2: Risk of bias of the included studies in the systematic review.
Note: AOW: Arthrocentesis with ozonized water; ARL: arthrocentesis with Ringer lactate; ASS: arthrocentesis with saline solution; CDI: Clinical dysfunction index; OT: ozone therapy; PL: placebo; PT: pharmacological therapy; VAS: Visual Analog Scale.

Table 2: Quality assessment of the included studies

Certainty assessment							No of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OT	Control	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Pain - Transdermal OT (follow up: range 1 wk to 4 wk; assessed with: VAS; Scale from: 0 to 100)												
4	Randomized trials	Very serious	Not serious	Not serious	Serious	None	88	85	–	SMD 0.18 lower (0.88 lower to 0.52 higher)	⊕○○○ Very low	Critical
Pain - Arthrocentesis OT (follow up: mean 1 mon; assessed with: VAS; Scale from: 0 to 100)												
3	Randomized trials	Very serious	Not serious	Not serious	Serious	None	60	60	–	SMD 1.47 lower (1.97 lower to 0.97 lower)	⊕○○○ Very low	Critical
Maximal Mouth Opening - Transdermal OT (follow up: range 1 wk to 4 wk; Scale from: 40 to 60)												
4	Randomized trials	Very serious	Not serious	Not serious	Serious	None	88	83	–	SMD 0.22 higher (0.11 lower to 0.55 higher)	⊕○○○ Very low	Critical
Maximal Mouth Opening - Arthrocentesis (follow up: median 1 yr; Scale from: 40 to 60)												
3	Randomized trials	Very serious	Not serious	Not serious	Serious	None	60	60	–	SMD 1.16 higher (0.77 higher to 1.55 higher)	⊕○○○ Very low	Critical

Note: CI: Confidence interval; SMD: standardized mean difference; OT: ozone therapy.

et al.[19] evaluated OT versus occlusal splint (OS) worn every night for 4 weeks. The team reported improvement of pain in both groups. Finally, Yamaner et al.[17] assessed OT versus sham OT. The team reported improvement of pain in the intervention group after one month of treatment.

On the other hand, there was evidence of the OT used in temporomandibular joint arthrocentesis. Hammuda et al.[20] and Elsholkamy[22] assessed pain with VAS in the TMJ with intraarticular disorder. The control group receives arthrocentesis with 2 mL of saline solution. Both studies reported improvement of pain with OT after 1 year. Also, Shabaan and Sabry[21] assessed VAS in TDM patients with anterior disc displacement without reduction. The control group receives arthrocentesis with 2 mL of Ringer lactate. Also, 875 mg of amoxicillin and 125 mg of clavulanic acid twice a day for 5 days and diclofenac potassium 50 mg three times daily were administered in both groups. The team reported improvement of pain using OT after one year.

Maximal mouth opening

Related to transdermal OT, Doğan et al.[16] reported no significant differences between therapies. On the other hand, Celakil et al.[18] reported an improvement in MMO after 2 weeks of OT treatment in comparison to sham OT. However, 2 years later, Celakil et al.[19] reported no significant differences between OT and occlusal splint. Finally, Yamaner et al.[17] reported no significant differences between treatments. On the other hand, concerning arthrocentesis with ozone, another three studies[20-22] reported an improvement in MMO in TMD treated with OT.

Clinical dysfunction outcomes

Only one study assessing clinical dysfunction index met inclusion criteria, Daif[23] evaluated the index of Helkimo in patients with bilateral internal derangement of the TMJ and disc displacement with reduction. The intervention group treated with OT was injected by 2 mL of ozone gas at 10 µg/mL of concentration into the articular fossa of the TMJ; the control group treated with pharmacological therapy received ibuprofen and chlorzoxazone three times per day for 2 weeks. The team reported improvement of clinical disfunction index in favor of OT after 2 weeks of treatment.

Meta-analyses

The results of the meta-analyses are shown in **Figure 3**.

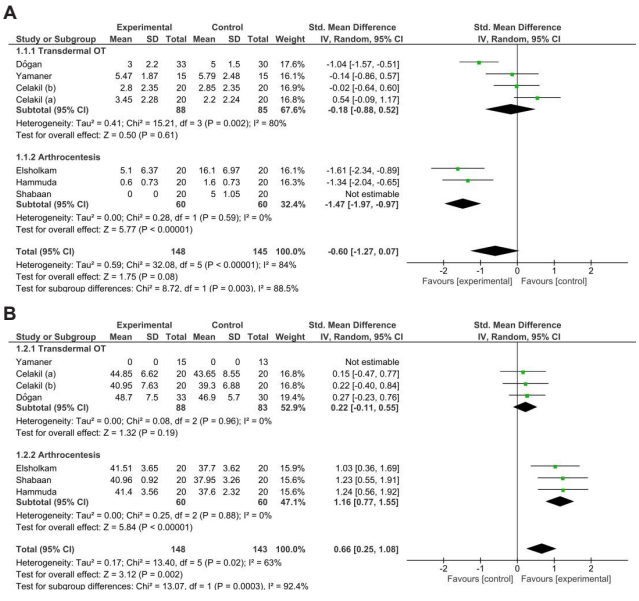

Figure 3: Meta-analyses of the efficacy of OT for pain (assessed by visual analog scale; A) and maximal mouth opening (B).Meta-analyses of the efficacy of OT for pain (assessed by visual analog scale; A) and maximal mouth opening (B).
Note: OT: Ozone therapy.

Discussion

The purpose of this review is to determine the efficacy of OT for the treatment of TMD. We included 8 studies with 234 participants suffering limited function and pain related to TMD. The plausible applicability of OT in the clinical practice of dentistry has been postulated due to the anti-hypoxic, antimicrobial, anti-inflammatory, and analgesic properties of the ozone.[24] This molecule has been tested to treat early carious lesions, tooth sensitivity, fissure lesions, dental plaque, periodontal pockets, ulcerations, herpetic lesions, and peri-implantitis. Additionally, ozone can be used as a cleaner of removable dentures and decontamination of dental instruments.[25]

OT can reduce pain because ozone increases the synthesis of superoxide dismutase, malondialdehyde, catalase, and the local release of catecholamines.[26] Besides, interleukin-6 and tumor necrosis factor-α levels in the synovial liquid of the TMJ are reduced.[27] This represents an increase in the threshold and a reduction in the responsiveness at the peripheral sensory nerve fibers.[28] This mechanism explains the results of the included studies that OT can diminish pain in TMD. Unfortunately, these clinical studies exhibited great heterogeneity, high risk of bias and low quality. Besides, two trials of transdermal OT[17,18] had only a placebo as a control group. This approach of comparing the effect of an intervention with placebo (untreated control group) leads to overestimations of the treatment effects, so the control group should be treated with a standard treatment rather than nothing.[29] This could explain the heterogeneity of the effect of the intervention found across the studies included in the meta-analysis. On the other hand, two studies had the best available therapy (occlusal splint[18] or pharmacological therapy[30]) as a control group, which could provide information about potential side effects.[31] Unfortunately, the follow-up in the included studies was heterogeneous and short (1 week[16] or 1 month[19]), and none of the studies aimed to report side effects. Similar issues were found in the studies related to arthrocentesis with ozonized water.

On the other hand, OT can improve angiogenesis and wound healing, which is exemplified by the fact that ozone accelerates cell cycle and increases the release of interferons and interleukins.[32] In addition, ozone can induce the synthesis of transforming growth factor β that is a regulator for inflammatory responses and the entire wound healing.[33] Therefore, the improvement in wound healing outcomes may be related to the recovery of function in TMD. However, the evidence points out that OT fails to improve MMO, due to the included studies showing heterogeneous results between them. Besides, only one study evaluated the clinical index but showed high risk of bias and low quality.

Nowadays, the dose, concentration, times, frequency, and recommendations for OT are still without consolidation. Therefore, more high-quality research with a low risk of bias to consolidate the knowledge concerning OT in dentistry is required.

OT can diminish pain and improve the MMO in TMD, particularly when OT is used in arthrocentesis. However, there is no conclusive evidence that OT acts as a superior treatment for TMD compared with occlusal splint and pharmacological therapy. The studies reviewed a broad range of comparators, application methods, ozone concentration, treatment sessions, and follow-up. Conclusions cannot be drawn due to the heterogeneity in the methodology applied, the small number of current investigations, and the few research teams in the field. Therefore, there is the need for more research with double-blind clinical trials that should be performed to consolidate the knowledge in the area before considering the use of OT in the treatment of TMD in clinical practice.

Acknowledgements
RTR and LAF thanks to CA-63 "Cuerpo académico Investigación en Salud"; LAF thanks to Investigadoras e Investigadores por México CONACyT program.

Author contributions
RTR and LAF conceived the review; RTR, MEMCG, LAFM, EUTR, RMNG and LAF collected and analyzed the data; and RTR and AFL led the writing. . All authors approved the final manuscript.

Conflicts of interest
All authors confirm that there no conflicts of interest that could inappropriately influence this work.

Availability of data and materials
All data generated or analyzed during this study are included in this published article and its supplementary information files.

Additional file
Additional Table 1: Characteristics and results of the included studies in the systematic review.

References

1. Østensjø V, Moen K, Storesund T, Rosén A. Prevalence of painful temporomandibular disorders and correlation to lifestyle factors among adolescents in Norway. *Pain Res Manag*. 2017;2017:2164825.
2. Manfredini D, Lombardo L, Siciliani G. Temporomandibular disorders and dental occlusion. A systematic review of association studies: end of an era? *J Oral Rehabil.* 2017;44:908-923.
3. Slade GD, Ohrbach R, Greenspan JD, et al. Painful temporomandibular disorder: decade of discovery from OPPERA studies. J Dent Res. 2016;95:1084-1092.
4. Dahlström L, Carlsson GE. Temporomandibular disorders and oral health-related quality of life. A systematic review. *Acta Odontol Scand.* 2010;68:80-85.
5. Osiewicz MA, Lobbezoo F, Loster BW, Loster JE, Manfredini D. Frequency of temporomandibular disorders diagnoses based on RDC/TMD in a Polish patient population. *Cranio.* 2018;36:304-310.
6. Kotiranta U, Forssell H, Kauppila T. Painful temporomandibular disorders (TMD) and comorbidities in primary care: associations with pain-related disability. *Acta Odontol Scand.* 2019;77:22-27.
7. Costa YM, Conti PC, de Faria FA, Bonjardim LR. Temporomandibular disorders and painful comorbidities: clinical association and underlying mechanisms. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2017;123:288-297.
8. Nguyen TT, Vanichanon P, Bhalang K, Vongthongsri S. Pain duration and intensity are related to coexisting pain and comorbidities present in temporomandibular disorder pain patients. *J Oral Facial Pain Headache.* 2019;33:205–212.
9. Hampton T. Improvements needed in management of temporomandibular joint disorders. *JAMA*. 2008;299:1119-1121.
10. Junior WCR, Esteves A, Serpeloni AL, Freitas JFB, Costa GdSFd. Use of acupuncture in the treatment of temporomandibular dysfunction. *Rev Int Acupunct.* 2019;13:76-81.
11. Ávila-Curiel BX, Gómez-Aguirre JN, Gijón-Soriano AL, Acevedo-Mascarúa AE, Argueta-Figueroa L, Torres-Rosas R. Complementary interventions for pain in patients with temporomandibular joint disorders: a systematic review. *Rev Int Acupunct.* 2020;14:151-159.
12. Zhou W, Hua L, Li M. Clinical efficacy of transforaminal percutaneous endoscopic lumbar discectomy combined with ozone therapy for the treatment of lumbar disc herniation: comparison with fenestration discectomy. A prospective study. *Invest Clin.* 2019;60:204-212.
13. Elvis AM, Ekta JS. Ozone therapy: a clinical review. *J Nat Sci Biol Med.* 2011;2:66-70.
14. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. *Wiley.* 2008.
15. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:l4898.
16. Doğan M, Ozdemir Doğan D, Düger C, et al. Effects of high-frequency bio-oxidative ozone therapy in temporomandibular disorder-related pain. *Med Princ Pract.* 2014;23:507-510.
17. Yamaner FE, Celakil T, Gökcen Roehlig B. Comparison of the efficiency of two alternative therapies for the management of temporomandibular disorders. *Cranio*. 2020. doi: 10.1080/08869634.2020.1727667.
18. Celakil T, Muric A, Gokcen Roehlig B, Evlioglu G, Keskin H. Effect of high-frequency bio-oxidative ozone therapy for masticatory muscle pain: a double-blind randomised clinical trial. *J Oral Rehabil*. 2017;44:442-451.
19. Celakil T, Muric A, Gökcen Roehlig B, Evlioglu G. Management of pain in TMD patients: Bio-oxidative ozone therapy versus occlusal splints. *Cranio*. 2019;37:85-93.
20. Hammuda AA, Hamed MS, Elsharrawy EA, Elsholkamy MA, Iskandar A. Use of ozone in temporomandibular joint arthrocentesis, clinical study. *J Am Sci.* 2013;9:508-513.
21. Shabaan AA, Sabry D. Efficiency of temporomandibular joint arthrocentesis with ozonated water in management of anterior disc displacement without reduction: a randomized clinical trial. *Egypt Dent J.* 2017;63:3133-3142.
22. Elsholkamy MA. A novel treatment for temporomandibular joint internal derangement: a randomized controlled clinical study. *Egypt Dent J*. 2018;64:3165-3172.
23. Daif ET. Role of intra-articular ozone gas injection in the management of internal derangement of the temporomandibular joint. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2012;113:e10-14.
24. Bocci VA. Scientific and medical aspects of ozone therapy. State of the art. *Arch Med Res*. 2006;37:425-435.
25. Azarpazhooh A, Limeback H. The application of ozone in dentistry: a systematic review of literature. *J Dent.* 2008;36:104-116.
26. Delaunois A, Segura P, Dessy-Doizé C, et al. Ozone-induced stimulation of pulmonary sympathetic fibers: a protective mechanism against edema. *Toxicol Appl Pharmacol.* 1997;147:71-82.
27. Yıldız A, Şehitoğlu MH, Karaboğa İ, Arıkan S. Ozone treatment for high-dose systemic Steroid-Induced retinal injury. *Cutan Ocul Toxicol.* 2020;39:274-280.
28. Arriaga-Pizano L, Gómez-Jiménez DC, Flores-Mejía LA, et al. Low back pain in athletes can be controlled with acupuncture by a catecholaminergic pathway: clinical trial. *Acupunct Med.* 2020;38:388-395.
29. Hróbjartsson A, Kaptchuk TJ, Miller FG. Placebo effect studies are susceptible to response bias and to other types of biases. *J Clin Epidemiol.* 2011;64:1223-1229.
30. Özalp Ö, Yıldırımyan N, Sindel A, Altay MA, Kişnişci RŞ. Evaluation of the short-term efficacy of transdermal ozone therapy in turkish patients with internal derangement of the temporomandibular joint. *Pesqui Bras Odontopediatria Clin Integr.* 2019;19:e4442.
31. Castro M. Placebo versus best-available-therapy control group in clinical trials for pharmacologic therapies: which is better? *Proc Am Thorac Soc.* 2007;4:570-573.
32. Stübinger S, Sader R, Filippi A. The use of ozone in dentistry and maxillofacial surgery: a review. *Quintessence Int.* 2006;37:353-359.
33. Fitzpatrick E, Holland OJ, Vanderlelie JJ. Ozone therapy for the treatment of chronic wounds: a systematic review. *Int Wound J.* 2018;15:633-644.

Date of submission: September 6, 2021
Date of decision: October 8, 2021
Date of acceptance: January 14, 2022
Date of web publication: December 22, 2022

Additional Table 1: Characteristics and results of the included studies in the systematic review

	Design	Population	Groups	Outcome measures	Results
Daif[23]	Randomized clinical trial	Patients with bilateral internal derangement of the TMJs and disc displacement with reduction (*n*=60)	G1: OT (*n*=30) G2: PT (*n*=30)	CDI, clinical outcome	**CDI (*n*):** Before G1: CDI 0=0; CDI I=2, CDI II=10, CDI III=18 G2: CDI 0=0, CDI I=1, CDI II=14, CDI III=15 2 wk after G1: CDI 0=11, Di I=5, CDI II=12, CDI III=2 G2: CDI 0=0, CDI I=7, CDI II=13, CDI III=10 **Clinical outcome (percentage):** Symptoms free G1: 87% G2: 33% Unchanged G1: 13% G2: 67%
Hammuda et al.[20]	Randomized clinical trial	Patients with temporomandibular joint internal derangement, disc displacement without reduction (*n*=30)	GI: AOW (*n*=15) G2: ASS (*n*=15)	MMO, VAS	**MMO (mean±SD):** G1: T0=28.733±3.918, T1=39.06±4.301, T2=35.267±5.035, T3=36.733±4.920, T4=37.733±3.955, T5=41.133±3.543, T6=41.400±3.562, T7=41.400±3.562 G2: T0=28.267±4.131, T1=40.667±2.637, T2=36.533±3.021, T3=37.400±3.180, T4=38.533±2.722, T5=38.733±2.712, T6=38.800±2.597, T7=37.600±2.324 **VAS (mean±SD):** G1: T0=5.933±1.223, T1=0.933±0.704, T2=2.133±0.640, T3=1.067±0.594, T4=0.400±0.507, T5=0.000±0.000, T6=0.467±0.640, T7=0.600±0.737 G2: T0=6.333±0.900, T1=1.600±0.632, T2=2.267±0.799, T3=0.600±0.910, T4=0.067±0.258, T5=0.333±0.488, T6=0.400±0.632, T7=1.600±0.737
Doğan et al.[16]	Randomized clinical trial	Patients with painful temporomandibular joint disorder (*n*=63)	G1: OT (*n*=33) G2: PT (*n*=30)	MMO, VAS	**MMO (mean±SD):** Pretreatment: *P*=0.907 G1:46.5±8.2, G2:46.3±6.0 Posttreatment: *P*=0.289 G1: 48.7±7.5, G2: 46.9±5.7 **VAS (mean±SD):** Pretreatment: *P*=0.199 G1: 6.3±2.1, G2: 6.9±1.4 Posttreatment: *P*=0.000 G1: 3.0±2.2, G2: 5.0±1.5
Celakil et al.[18]	Randomized clinical trial	Female patients with myofascial pain dysfunction syndrome (*n*=40)	G1: OT (*n*=20) G2: Sham OT (*n*=20)	Maximum unassisted opening (MUO), left lateral extrusion (LLE), right lateral extrusion (RLE), protrusion, VAS T0= Before the first treatment, T1=1 mon after the last application session, T2=3 mon after the last application session	**MUO (mean±SD (median)):** G1: T0=42.65±8.39 (44), T1=45.00±7.17 (45), T2=44.85±6.62 (45); *P*=0.005 G2: T0=44.20±7.38 (45), T1=45.70±7.47 (46), T2=43.65±8.55 (45); *P*=0.111 Between groups T0: *P*=0.539, T1: *P*=0.764, T2: *P*=0.623 **LLE (mean±SD (median)):** G1: T0=7.30±2.47 (7), T1=9.20±2.57 (9.5), T2=9.15±2.23 (9); *P*=0.001 G2: T0=6.60±3.02 (6), T1=7.55±2.96 (8), T2=7.70±3.06 (7); *P*=0.125 Between groups T0: *P*=0.427, T1: *P*=0.427, T2: *P*=0.095 **RLE (mean±SD (median)):** G1: T0=6.95±2.56 (6), T1=8.85±2.08 (9), T2 8.90±1.77 (9); *P*=0.001 G2: T0=6.10±2.47 (5.5), T1=7.65±2.52 (8), T2=6.85±2.41 (7); *P*=0.008 Between groups T0: *P*=0.366, T1: *P*=0.118, T2: *P*=0.003 **Protrusion (mean±SD (median)):** G1: T0=6.95±2.16 (7), T1= 7.45±2.31 (7), T2=7.75±1.80 (8.5); *P*=0.264 G2: T0=6.45±2.28 (7), T1= 8.10±2.34 (9), T2= 7.25±2.02 (8); *P*=0.001 Between groups T0: *P*=0.622, T2: *P*=0.330, T3: *P*=0.240 **VAS (mean±SD (median)):** G1: T0=6.75±1.45 (7), T1=4.20±2.09 (5), T2=3.45±2.28 (3); *P*=0.001 G2: T0=6.95±1.82 (7), T1=2.80±2.35 (2), T2=2.20±2.24 (1); *P*=0.001 Between groups T0: *P*=0.726, T1: *P*=0.057, T2: *P*=0.040

Additional Table 1: Continued

	Design	Population	Groups	Outcome measures	Results
Shabaan and Sabry[21]	Randomized clinical trial	TDM patients with anterior disc displacement without reduction (*n*=40)	G1: AOW (*n*=20) G2: ARL (*n*=20)	MMO, VAS, IL-6	**MMO (mean±SD):** Pre-operative: *P*=0.700 G1: 18.18±1.63, G2: 17.98±1.70 1 wk: *P*=0.961 GI: 23.23±1.71, G2: 23.26±2.13 1 mon: *P*=0.993 G1: 36.66±1.13, G2: 36.65±2.30 3 mon: *P* < 0.001 G1: 40.74±0.75, G2: 39.65±0.88 6 mon: *P* < 0.001 G1: 41.02±0.80, G2: 39.73±0.93 12 mon: *P* < 0.001 G1: 40.96±0.92, G2: 37.95±3.26 *P*(group): G1: *P* < 0.001, G2: *P* < 0.001 **VAS (mean±SD):** Pre-operative: *P*=0.700 G1: 9.65±1.63, G2: 17.98±1.70 1 wk: *P* < 0.001 G1: 1.10±1.07, G2: 8.30±1.03 1 mon: *P* < 0.001 GI: 0.15±0.37, G2: 5.80±1.82 3 mon: *P* < 0.001 G1: 0.00±0.00, G2: 1.30±1.34 6 mon: *P* < 0.019 G1: 0.00±0.00, G2: 0.50±1.05 12 mon: *P* < 0.038 G1: 0.00±0.00, G2: 1.56±3.19 *P*(group): G1: *P* < 0.001, G2: *P* < 0.001 IL-6 (mean±SD): Pre-operative: *P*=1.000 GI: 10.18±2.25, G2: 10.18±2.25 Immediate post-operative: *P* < 0.001 G1: 1.29±0.61, G2: 3.39±1.29 6 mon: *P* < 0.001 G1: 1.63±0.57, G2: 4.69±1.54 *P*(group): G1: *P* < 0.001, G2: *P* < 0.001 **MMO (mean±SD):** Pre-operative – 1 wk: *P*=0.683 G1: 28.4±8.6, G2: 30.3±10.3 Pre-operative – 1 mon: *P*=0.705 G1: 103.1±18.5, G2: 105.7±23.3 Pre-operative – 3 mon: *P*=0.610 G1: 125.7±19.9, G2: 122.4±20.8 Pre-operative – 6 mon: *P*=0.488 G1: 127.2±19.3, G2: 122.8±20.5 Pre-operative – 12 mon: *P*=0.103 G1: 126.8±19.1, G2: 113.4±30.3 **VAS (mean±SD):** Pre-operative – 1 wk: *P* < 0.001 G1: –88.8±10.81, G2: –13.7±4.2 Pre-operative – 1 mon: *P* < 0.001 G1: –98.4±3.8, G2: –39.8±11.8 Pre-operative – 3 mon: *P* < 0.001 GI: –100.0±0.0, G2: –86.5±13.9 Pre-operative – 6 mon: *P*=0.019 G1: –100.0±0.0, G2: –94.9±10.7 Pre-operative – 12 mon: *P*=0.038 G1: –100.0±0.0, G2: –83.7±33.6 **IL-6 (mean±SD):** Pre-operative – immediate post-operative: *P* < 0.001 G1: –87.0±6.3, G2: –64.9±15.4 Pre-operative – 6 mon: *P* < 0.001 G1: –83.4±6.6, G2: –52.7±14.9
Elsholkamy[22]	Randomized Clinical trial	Patients with limited function and pain related to the TMJ (*n*=30)	G1: AOW (*n*=15) G2: ASS (*n*=15)	VAS, MMO	**VAS (mean±SD):** G1: Pre-operative: 6.133±1.069, immediate post-operative: 0.943±0.714 (*P* < 0.001), 2 d postoperatively: 2.853±0.640 (*P* < 0.001), 1 mon postoperatively: 0.000±0.000 (*P* < 0.001), 6 mon postoperatively: 0.256±0.640 (*P* < 0.001), 1 yr postoperatively: 0.518±0.637 (*P* < 0.001). G2: Pre-operative: 7.213±0.859, immediate post-operative: 1.712±0.613 (*P* < 0.001), 2 d postoperatively: 2.561±0.659 (*P* < 0.001), 1 mon postoperatively: 0.335±0.338 (*P* < 0.001), 6 mon postoperatively: 0.456±0.638 (*P* < 0.001), 1 yr postoperatively: 1.618±0.697 (*P* < 0.001) **MMO (mean±SD):** G1: Pre-operative 28.713±3.189, immediate post-operative: 38.911±4.123 (*P* < 0.001), 2 d postoperatively: 34.247±5.023 (*P* < 0.001), 1 mon postoperatively: 40.933±3.345 (*P* < 0.001), 6 mon postoperatively: 41.512±3.652 (*P* < 0.001), 1 yr postoperatively: 41.512±3.652 (*P* < 0.001) G2: Pre-operative: 29.134±4.243, immediate post-operative: 40.689±2.537 (*P* < 0.001), 2 d postoperatively: 36.233±3.120 (*P* < 0.001), 1 mon postoperatively: 38.834±2.217 (*P* < 0.001), 6 mon postoperatively: 38.917±2.357 (*P* < 0.001), 1 yr postoperatively: 37.700±3.627 (*P* < 0.001)

Additional Table 1: Continued

	Design	Population	Groups	Outcome measures	Results
Celakil et al.[19]	Randomized clinical trial	Patients with temporomandibular disorder pain (*n*=40)	G1: OT (*n*=20) G2: OS (*n*=20)	APP, UOP, MUO, MAO, LLE, RLE, PRO, PPT, VAS	**APP (mean±SD (median)):** G1: *P*=0.039 Before: 3.7±0.65 (4), After 3.1±1.07 (3) G2: *P*=0.010 Before: 3.5±0.60 (4), After 2.9±0.78 (3) Intergroups G1: *P*=0.318, G2: *P*=0.503 **UOP (mean±SD (median)):** G1: *P*= 0.001 Before: 37.45±8.54 (39.5), After: 40.95±7.63 (41.5), Before-After: 11.06±13.00 (10.7). G2: *P*=0.001 Before: 33.40±7.21 (33.5), After: 39.30±6.88 (41.5), Before-After: 19.50±14.32 (17.1) Between groups Before: *P*=0.149, After: *P*=0.495, Before-After: *P*=0.038 **MUO (mean±SD (median)):** G1: *P*=0.003 Before: 42.65±8.39 (44), After: 45.00±7.17 (45), Before-After: 6.72±8.54 (5.3). G2: *P*=0.001 Before: 41.50±6.88 (43.5), After: 43.40±6.06 (45.5), Before-After: 5.13±5.07 (2.6) Between groups Before: *P*=0.547, After: *P*=0.450, Before-After: *P*=0.678 **MAO (mean±SD (median)):** G1: P=0.003 Before: 45.00±8.53 (47), After: 47.40±6.72 (48), Before-After: 6.81±10.61 (4.7) G2: *P*=0.002 Before: 43.20±6.57 (44.5), After: 44.45±5.91 (45.5), Before-After: 3.27±4.02 (2.2) Between groups Before: *P*=0.678, After: *P*=0.383, Before-After: *P*=0.174 **LLE (mean±SD (median)):** G1: *P*=0.001 Before: 7.30±2.47 (7), After: 9.20±2.57 (9.5), Before-After: 30.47±26.42 (23.6). G2: *P*=0.179 Before: 8.05±2.56 (8), After: 8.45±1.90 (8), Before-After: 15.57±47.57 (0). Between groups Before: *P*=0.265, After: *P*=0.301, Before-After: *P*=0.007 **RLE (mean±SD (median)):** G1: *P*=0.002 Before: 6.95±2.56 (6), After: 8.85±2.08 (9), Before-After: 39.51±48.15 (26.8). G2: *P*=0.180 Before: 8.15±2.41 (8.5), After: 8.65±1.63 (9), Before-After: 12.77±31.67 (0). Between groups Before: *P*=0.136, After: *P*=0.737, Before-After: *P*=0.033 **PRO (mean±SD (median)):** G1: *P*=0.383 Before: 6.95±2.16 (7), After: 7.45±2.31 (7), Before-After: 14.52±41.46 (5.6). G2: *P*=0.577 Before: 6.80±1.54 (6.5), After: 6.85±1.5 (7), Before-After: 1.25±7.78 (0). Between groups Before: *P*=0.802, After: *P*=0.335, Before-After: *P*=0.495 **PPT (mean±SD (median)):** G1: *P*=0.014 Before 23.50±6.10 (22), After 26.96±9.05 (23.5), Before-After: 14.84±24.99 (9.7) G2: *P*=0.001 Before: 23.50±6.10 (22) 24.26±6.09 (23.8), After: 31.81±5.13 (31.1), Before-After 34.29±19.42 (31.9) Between groups Before: *P*=0.693, After: *P*=0.046, Before-After: *P*=0.005 **Masseter (mean±SD (median)):** G1: *P*=0.001 Before: 16.05±4.84 (15.3), After: 20.78±7.31 (17.8), Before-After: 30.89±32.04 (26.5) G2: *P*=0.001 Before 16.86±3.89 (15.7), After: 25.29±4.52 (24.3), Before-After: 53.13±27.13 (45.1) Between groups Before: *P*=0.005, After: *P*=0.369, Before-After: *P*=0.024 **Lateral pole (mean±SD (median)):** G1: *P*=0.001 Before 16.05±4.84 (15.3) 17.85±4.60 (17.5), After 23.15±9.25 (21), Before-After 27.07±28.23 (31.5) G2: *P*=0.001 Before: 18.60±4.57 (17), After: 24.55±4.49 (24), Before-After: 35.46±25.57 (31.4) Between groups Before: *P*=0.659, After: *P*=0.547, Before-After: *P*=0.529 **VAS (mean±SD (median)):** G1: *P*= 0.001 Before: 6.95±1.82 (7), After: 2.80±2.35 (2), Before-After: −57.43±37.20 (−61.3) G2: *P*=0.001 Before 6.65±1.81 (6.5), After: 2.85±1.39 (3), Before-After: −52.40±27.95 (−56.3) Between groups Before: *P*=0.659, After: *P*=0.529, Before-After: *P*=0.495

Additional Table 1: Continued

	Design	Population	Groups	Outcome measures	Results
Yamaner et al.[17]	Randomized clinical trial	Patients with disc displacement with reduction (*n*=61) CMM opening pattern: *n*(%)	G1: LAT (*n*=18) G2: OT (*n*=15) G3: Sham LAT (*n*=13) G4: Sham OT (*n*=15)	CMM, PP, PPT, UOP, MUO, MAO, VAS	**CMM opening pattern (*n*(%)):** G1: before: S: 8(53.3), ULD: 2(13.3), CD: 5 (33.3); 1 mon later: S: 9(60), ULD: 1(67), CD: 5 (33.3); 3 mon later: S: 9(60), ULD: 1(67), CD: 5 (33.3); 6 mon later: S: 9(60), ULD: 1(67), CD: 5 (33.3) G2: before: S: 7(38.9), ULD: 4(22.2), CD: 7(38.9); 1 mon later: S: 12(66.7), ULD: 2(11.1), CD: 4(22.2); 3 mon later: S: 12(66.7), ULD: 3(16.7), CD: 3(16.7); 6 mon later: S: 12(66.7), ULD: 2(11.1), CD: 4(22.2) G3: before: S: 11(68.8), ULD: 0(0), CD: 5 (31.3); 1 mon later: S: 10(62.5), ULD: 1(6.3), CD: 5 (31.3); 3 mon later: not evaluated, 6 mon later: not evaluated. G4: before: S: 7(53.8), ULD: 2(15.4), CD: 4 (30.4); 1 mon later: S: 8(61.5), ULD: 1(7.7), CD: 4 (30.8); 3 mon later: not evaluated, 6 mon later: not evaluated **CMM Joint sounds (open) (*n*(%)):** G1: before: none: 0(0), CL: 14(70), CR: 6(30); 1 mon later: before: none: 3(15), CL: 11(55), CR: 6(30); 3 mon later: before: none: 3(15), CL: 11(55), CR: 6(30); 6 mon later: before: none: 4(20), CL: 10(50), CR: 6(30) G2: before: none: 0(0), CL: 19(95), CR: 1(5); 1 mon later: before: none: 1(5), CL: 15(75), CR: 4(20); 3 mon later: before: none: 1(5), CL: 15(75), CR: 4(20); 6 mon later: before: none: 0(0), CL: 15(75), CR: 5(25) G3: before: none: 0(0), CL: 16(80), CR: 4(20); 1 mon later: before: none: 3(15), CL: 14(70), CR: 3(15); 3 mon later: not evaluated, 6 mon later: not evaluated G4: before: none: 0(0), CL: 19(95), CR: 1(5); 1 mon later: before: none: 0(0), CL: 17(85), CR: 3(15); 3 mon later: not evaluated, 6 mon later: not evaluated **CMM Joint sounds (close) (*n*(%)):** G1: before: none: 3(15), CL: 11(55), CR: 6(30); 1 mon later: before: none: 4(20), CL: 10(50), CR: 6(30); 3 mon later: before: none: 4(20), CL: 11(55), CR: 5(25); 6 mon later: before: none: 4(20), CL: 10(50), CR: 6(30) G2: before: none: 3(15), CL: 13(65), CR: 4(20); 1 mon later: before: none: 2(10), CL: 9(45), CR: 9(45); 3 mon later: before: none: 3(15), CL: 10(50), CR: 7(35); 6 mon later: before: none: 2(10), CL: 12(60), CR: 6(30) G3: before: none: 3(15), CL: 12(60), CR: 5(25); 1 mon later: before: none: 6(30), CL: 9(45), CR: 5(25); 3 mon later: not evaluated, 6 mon later: not evaluated G4: before: none: 2(10), CL: 14(70), CR: 4(20); 1 mon later: before: none: 11(55), CL: 5(25), CR: 3(15); 3 mon later: not evaluated, 6 mon later: not evaluated **CMM Joint sounds (excursion) (*n*(%)):** G1: before: none: 7(35), CL: 11(55), CR: 2(10); 1 mon later: before: none: 9(45), CL: 9(45), CR: 2(10); 3 mon later: before: none: 8(40), CL: 11(55), CR: 1(5); 6 mon later: before: none: 8(40), CL: 11(55), CR: 1(5) G2: before: none: 6(30), CL: 13(65), CR: 1(5); 1 mon later: before: none: 4(20), CL: 13(65), CR: 3(15); 3 mon later: before: none: 5(25), CL: 13(65), CR: 2(10); 6 mon later: before: none: 6(30), CL: 11(55), CR: 3(15) G3: before: none: 2(10), CL: 14(70), CR: 4(20); 1 mon later: before: none: 10(50) ($P < 0.05$), CL: 8(40) ($P < 0.05$), CR: 2(10) ($P < 0.05$); 3 mon later: not evaluated, 6 mon later: not evaluated G4: before: none: 5(25), CL: 11(55), CR: 4(20); 1 mon later: before: none: 5(25), CL: 11(55), CR: 4(20); 3 mon later: not evaluated, 6 mon later: not evaluated **CMM Joint sounds (protrusion) (*n*(%)):** G1: before: none: 7(35), CL: 10(50), CR: 3(15); 1 mon later: before: none: 9(45), CL: 9(45), CR: 2(10); 3 mon later: before: none: 8(40), CL: 10(50), CR: 2(10); 6 mon later: before: none: 8(40), CL: 10(50), CR: 2(10) G2: before: none: 9(45), CL: 11(55), CR: 0(0); 1 mon later: before: none: 6(30), CL: 11(55), CR: 5(15); 3 mon later: before: none: 6(30), CL: 11(55), CR: 3(15); 6 mon later: before: none: 8(40), CL: 10(50), CR: 2(10) G3: before: none: 8(40), CL: 9(45), CR: 3(15); 1 mon later: before: none: 10(50), CL: 6(30), CR: 4(20); 3 mon later: not evaluated, 6 mon later: not evaluated G4: before: none: 4(20), CL: 11(55), CR: 5(25); 1 mon later: before: none: 5(25), CL: 11(55), CR: 4(20); 3 mon later: not evaluated, 6 mon later: not evaluated **RC (*n*(%)):** G1: before: 18(90); 1 mon later: 16(80); 3 mon later: 16(80); 6 mon later: 16(80) G2: before: 17(85); 1 mon later: 18(90); 3 mon later: 18(90); 6 mon later: 18(90) G3: before: 16(80); 1 mon later: 14(70); 3 mon later: not evaluated; 6 mon later: not evaluated. G4: before: 18(90); 1 mon later: 16(80); 3 mon later: not evaluated; 6 mon later: not evaluated. **PP (mean±SD):** ***TP***: G1: Before: 0.35±0.75, 1 mon later: 0.25±0.55, 3 mon later: 0.15±0.49 ($P < 0.05$), A 6 mon later: 0.15±0.49 ($P < 0.05$) G2: Before: 0.70±0.86, 1 mon later: 0.45±0.60, 3 mon later: 0.30±0.57 ($P < 0.05$), A 6 mon later: 0.30±0.47 ($P < 0.05$) G3: Before: 0.65±0.67, 1 mon later: 0.45±.069, 3 mon later: not evaluated, 6 mon later: not evaluated. G4: Before: 0.35±0.67, 1 mon later: 0.35±0.75, 3 mon later: not evaluated, 6 mon later: not evaluated. ***TM*:** G1: Before: 0.60±0.82, 1 mon later: 0.45±0.69, 3 mon later: 0.25±0.55 ($P < 0.05$), 6 mon later: 0.20±0.41 ($P < 0.05$) G2: Before: 0.80±0.89, 1 mon later: 0.65±0.75, 3 mon later: 0.60±075, 6 mon later: 0.50±0.69 G3: Before: 1.05±1.00, 1 mon later: 0.95±0.69, 3 mon later: not evaluated, 6 mon later: not evaluated. G4: Before: 1.00±1.03, 1 mon later: 0.90±0.85, 3 mon later: not evaluated, 6 mon later: not evaluated. ***TA*:** G1: Before: 1.25±1.02, 1 mon later: 1.00±0.65, 3 mon later: 0.90±0.64, 6 mon later: 0.65±0.67 ($P < 0.01$) G2: Before: 1.05±0.83, 1 mon: 0.80±0.70, 3 mon later: 0.90±0.79, 6 mon later: 0.70±0.57 G3: Before: 1.35±0.99, 1 mon later: 1.00±0.79, 3 mon later: not evaluated, 6 mon later: not evaluated. G4: Before: 1.05±0.76, 1 mon later: 0.75±0.91, 3 mon later: not evaluated, 6 mon later: not evaluated.

Additional Table 1: Continued

Design	Population	Groups	Outcome measures	Results
				***MS*:** G1: Before: 1.80±1.06, 1 mon later: 1.60±0.94, 3 mon later: 1.40±0.94, 6 mon later: 0.80±0.89 ($P < 0.01$) G2: Before: 1.35±0.99, 1 mon later: 1.05±1.10, 3 mon later: 0.85±1.04 ($P < 0.05$), 6 mon later: 0.80±0.89 ($P < 0.05$) G3: Before: 1.30±0.98, 1 mon later: 1.15±0.93, 3 mon later: not evaluated, 6 mon later: not evaluated. G4: Before: 1.15±0.88, 1 mon later: 1.00±0.86, 3 mon later: not evaluated, 6 mon later: not evaluated. ***MM*:** G1: Before: 1.80±1.06, 1 mon later: 1.60±0.94, 3 mon later: 1.40±0.94, 6 mon later: 0.80±0.89 ($P < 0.01$) G2: Before: 1.35±0.99, 1 mon later: 1.05±1.10, 3 mon later: 0.85±1.04 ($P < 0.05$), 6 mon later: 0 0.80±0.89 ($P < 0.05$) G3: Before: 1.30±0.98, 1 mon later: 1.15±0.93, 3 mon later: –, 6 mon later: – G4: Before: 1.15±0.88, 1 mon later: 1.00±0.86, 3 mon later: not evaluated, 6 mon later: not evaluated. ***MI*:** G1: Before: 1.20±0.89, 1 mon later: 1.20±0.83, 3 mon later: 0.95±0.83, 6 mon later: 0.60±0.82 ($P < 0.05$) G2: Before: 1.55±1.19, 1 mon later: 1.05±0.69 ($P < 0.05$), 3 mon later: 0.90±0.72 ($P < 0.01$), 6 mon later: 0.80±0.70 ($P < 0.01$) G3: Before: 1.00±0.92, 1 mon later: 0.85±1.04, 3 mon later: –, 6 mon later: – G4: Before: 11.20±0.95, 1 mon later: 0.70±0.86 ($P < 0.05$), 3 mon later: not evaluated, 6 mon later: not evaluated. ***LP*:** G1: Before: 1.50±0.89, 1 mon later: 1.15±0.93, 3 mon later: 0.85±0.93 ($P < 0.01$), 6 mon later: 0.70±0.66 ($P < 0.01$) G2: Before: 2.05±1.05, 1 mon later: 1.50±0.95 ($P < 0.05$), 3 mon later: 1.15±0.75 ($P < 0.01$), 6 mon later: 1.05±0.76 ($P < 0.01$) G3: Before: 1.90±0.97, 1 mon later: 1.25±1.07 ($P < 0.01$), 3 mon: not evaluated, 6 mon later: not evaluated G4: Before: 1.30±1.08, 1 mon later: 1.25±1.12, 3 mon later: not evaluated, 6 mon later: not evaluated ***PA*:** G1: Before: 0.85±1.04, 1 mon later: 0.65±0.81, 3 mon later: 0.55±0.83, 6 mon later: 0.25±0.55 ($P < 0.01$) G2: Before: 0.95±1.15, 1 mon later: 0.80±0.95, 3 mon later: 0.50±0.83, 6 mon later: 0.30±0.47 ($P < 0.05$) G3: Before: 0.55±0.76, 1 mon later: 0.35±0.75, 3 mon later: not evaluated, 6 mon later: not evaluated G4: Before: 0.25±0.55, 1 mon later: 0.35±0.49, 3 mon later: not evaluated, 6 mon later: not evaluated **PPT (mean±SD):** ***TP*:** G1: Before: 39.10±2.29, 1 mon later: 39.15±2.46, 3 mon later: 39.15±2.46, 6 mon later: 39.15±3.36 G2: Before: 36.85±5.94, 1 mon later: 37.10±4.69, 3 mon later: 36.90±4.59, 6 mon later: 37.30 ± 4.75 G3: Before: 37.45±5.00, 1 mon later: 37.45±5.63, 3 mon later: not evaluated, 6 mon later: not evaluated. G4: Before: 39.60±1.79, 1 mon later: 36.70±4.80 (P<0.05), 3 mon later: not evaluated, 6 mon later: not evaluated. ***TM*:** G1: Before: 39.00±2.08, 1 mon later: 38.35±2.94, 3 mon later: 38.75±3.09, 6 mon later: 38.30±4.64 G2: Before: 36.80±5.69, 1 mon later: 36.40±4.97, 3 mon later: 36.95±4.65, 6 mon later: 37.90±4.17 G3: Before: 36.80±4.24, 1 mon later: 37.05±4.37, 3 mon later: not evaluated, 6 mon later: not evaluated. G4: Before: 38.60±3.05, 1 mon later: 37.25±5.01, 3 mon later: not evaluated, 6 mon later: not evaluated. ***TA*:** G1: Before: 33.75±3.54, 1 mon later: 34.35±3.51, 3 mon later: 34.20±4.05, 6 mon later: 34.65±5.83 G2: Before: 32.90±6.09, 1 mon later: 34.65±4.11, 3 mon later: 35.60±4.11 ($P < 0.05$), 6 mon later: 36.45±4.25 ($P < 0.05$) G3: Before: 32.85±5.53, 1 mon later: 32.95±6.53, 3 mon later: not evaluated, 6 mon later: not evaluated. G4: Before: 35.75±4.59, 1 mon later: 33.30±6.59, 3 mon later: not evaluated, 6 mon later: not evaluated. ***MS*:** G1: Before: 27.60±8.27, 1 mon later: 29.90±6.66, 3 mon later: 28.85±6.02, 6 mon later: 30.50±7.04 G2: Before: 29.05±9.67, 1 mon later: 30.55±6.89, 3 mon later: 31.45±6.91, 6 mon later: 29.80±6.69 G3: Before: 28.15±6.51, 1 mon later: 27.15±8.63, 3 mon later: not evaluated, 6 mon later: not evaluated. G4: Before: 32.20±6.21, 1 mon later: 30.25±7.97, 3 mon later: not evaluated, 6 mon later: not evaluated. ***MM*:** G1: Before: 24.25±4.80, 1 mon later: 26.30±5.89, 3 mon later: 26.40±4.96, 6 mon later: 27.75±6.90 G2: Before: 22.10±5.86, 1 mon later: 24.25±7.33 ($P < 0.05$), 3 mon later: 25.60±7.30 ($P < 0.01$), 6 mon later: 27.60±7.76 ($P < 0.01$) G3: Before: 24.60±6.72, 1 mon later: 25.00±7.85, 3 mon later: not evaluated, 6 mon later: not evaluated. G4: Before: 27.15±5.78, 1 mon later: 23.35±5.61 ($P < 0.05$), 3 mon later: not evaluated, 6 mon later: not evaluated ***MI*:** G1: Before: 26.30±6.82, 1 mon later: 28.60±7.09 ($P < 0.05$), 3 mon later: 28.15±6.03, 6 mon later: 29.70±7.33 ($P < 0.05$) G2: Before: 24.30±7.60, 1 mon later: 24.75±7.26, 3 mon later: 26.80±6.76, 6 mon later: 27.00±9.38 G3: Before: 26.25±6.49, 1 mon later: 25.35±7.29, 3 mon later: not evaluated, 6 mon later: not evaluated. G4: Before: 27.05±6.35, 1 mon later: 25.85±6.91, 3 mon later: not evaluated, 6 mon later: not evaluated. ***LP*:** G1: Before: 27.60±4.77, 1 mon later: 28.50±5.36, 3 mon later: 28.40±5.59, 6 mon later: 29.50±6.24 G2: Before: 25.35±7.43, 1 mon later: 26.35±7.26, 3 mon later: 29.45±6.95 (P<0.01), 6 mon later: 30.20±6.11 ($P < 0.01$) G3: Before: 27.05±5.82, 1 mon later: 28.65±7.01, 3 mon later: not evaluated, 6 mon later: not evaluated G4: Before: 31.55±5.75, 1 mon later: 30.05±8.22, 3 mon later: not evaluated, 6 mon later: not evaluated **UOP (mm) (mean±SD):** G1: Before: 40.67±6.37, 1 mon later: 41.00±6.12, 3 mon later: 41.40±6.10, 6 mon later: 41.60±6.50 G2: Before: 40.83±5.88, 1 mon later: 39.78±5.76 (P<0.05), 3 mon later: 40.83±5.88, 6 mon later: 41.00±5.89 G3: Before: 41.62±3.30, 1 mon later: 41.13±4.26, 3 mon later: not evaluated, 6 mon later: not evaluated G4: Before: 39.15±4.51, 1 mon later: 39.92±5.02, 3 mon later: not evaluated, 6 mon later: not evaluated **MUO (mm) (mean±SD):** G1: Before: 44.33±6.80, 1 mon later: 44.47±6.62, 3 mon later: 44.67±6.29, 6 mon later: 44.87±6.59 G2: Before: 44.33±5.75, 1 mon later: 43.61±5.81, 3 mon later: 43.67±6.23, 6 mon later: 43.89±6.48 G3: Before: 45.25 ± 4.04, 1 mon later: 44.19 ± 5.06, 3 mon later: not evaluated, 6 mon later: not evaluated G4: Before: 41.38 ± 4.74, 1 mon later: 42.15 ± 4.76, 3 mon later: not evaluated, 6 mon later: not evaluated **MAO (mm) (mean±SD):** G1: Before: 48.00±6.82, 1 mon later: 47.80±6.55, 3 mon later: 47.60±6.63, 6 mon later: 48.00±6.51 G2: Before: 46.72±4.86, 1 mon later: 46.56±4.88, 3 mon later: 46.61±5.19, 6 mon later: 46.83±5.91 G3: Before: 47.25±3.89, 1 mon later: 46.88±5.58, 3 mon later: not evaluated, 6 mon later: not evaluated. G4: Before: 43.69±5.57, 1 mon later: 40.92±11.98, 3 mon later: not evaluated, 6 mon later: not evaluated **VAS (mean±SD):** G1: Before: 7.45±1.96, 1 mon later: 5.87±2.07, 3 mon later 5.87±2.39, 6 mon later 5.00±1.90, Before-1 mon later (P=0.049), Before-3 mon later (P=0.049), Before-6 mon later (P=0.013) G2: Before: 6.99±2.01, 1 mon later: 5.47±1.87, 3 mon later: 5.39±1.91, 6 mon later: 4.75±2.04, Before-1 mon later (P=0.035), Before-3 mon later (P=0.024), Before-6 mon later (P=0.009) G3: Before: 7.32±1.39, 1 mon later: 6.26±1.89, Before-1 mon later (P=0.021) G4: Before: 6.99±1.84, 1 mon later: 5.79±2.48, Before-1 mon later (P=0.064) Between groups Before: P=0.802, 1 mon later: P=0.696, 3 mon later: P=0.487, 6 mon later: P=0.691

Note: AOW: arthrocentesis with ozonized water; APP: average pain palpation; ARL: arthrocentesis with Ringer lactate; ASS: arthrocentesis with saline solution; CD: Corrected deviation; CDI: Clinical dysfunction index; CL: Clicking; CMM: mandibular movement patterns; CR: Crepitus; IL-6: interleukin 6; LAT: laser therapy; LP: Lateral pole, outside; MAO: maximum assisted opening; MI: Masseter inferior; MM: Masseter middle; MMO: maximal mouth opening; MS: Masseter superior; MUO: maximum unassisted opening; OS: occlusal splint; OT: ozone therapy; PA: Posterior attachment, inside ear; PP: Pain on palpation; PPT: Pressure pain threshold examination; PT: pharmacological therapy; RC: Reciprocal clicking; S: straight; TA: Temporalis anterior; TM: Temporalis middle; TP: Temporalis posterior; ULD: uncorrected lateral deviation; UOP: unassisted opening without pain; VAS: Visual Analog Scale.