Universidad Europea VALENCIA

Grado en ODONTOLOGÍA

Trabajo Fin de Grado

Curso 2021-22

Comparison of the effectiveness between peri/ intra-articular injections and conventional treatments in patients with temporomandibular disorders' symptoms:

A systematic review

Presentado por: Laetitia MASSÉ

Tutor: Ana CANDEL TOMÁS

Campus de Valencia
Paseo de la Alameda, 7
46010 Valencia
universidadeuropea.com

Universidad Europea VALENCIA

TABLE OF CONTENT

ACKNOWLEDGMENT

First and foremost, I would like to thank my thesis tutor Dra. Ana Candel Tomás of the European University of Valencia for her time, thoughtful comment and recommendations throughout this academic year.

Further, I would like to express my gratitude to Dra. Maria Gracia Sarrión Pérez of the European University of Valencia for all the considerate guidance.

Finally, I could not forget to thank my parents and my fiancé Salim Bouchibi for all the unconditional support.

SIGNS

TMJ: Temporomandibular joint.

TMD: Temporomandibular disorder.

RDC/TMD: Research Diagnostic Criteria for temporomandibular disorders.

DC/ TMD: Diagnostic criteria for temporomandibular disorders.

MRI: Magnet Resonance Imaging.

CT: Computed tomography.

GCPS: Graded Chronic Pain Scale.

JFLS: Jaw Functional Limitation Scale Short-form.

PHQ-4: Patient Health Questionaire-4.

OBC: Oral Behavioral Checklist.

IMMPACT: Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials.

GAD-7: Generalized-Anxiety Disorder-7.

IAI: intra-articular injections.

NSAID: Non-steroidal anti-inflammatories.

TENS: Transcutaneous electrical nerve stimulation.

LLT: Low-level laser therapy.

BoNT-A: Botulinum toxin type A.

HA: Hyaluronic Acid.

PRP: Platelet Rich Plasma.

RCT: Randomized Controlled Trial.

CASP: Critical Appraisal Skills Program.

VAS: Visual Analogue Scale

NRS: Numeric Rating Scale

MMO: Maximum Mouth Opening

MIO: Maximal Interincisal Opening

ABSTRACT

Introduction: Temporomandibular disorders (TMD) is a generic term to describe a group of related musculoskeletal signs and symptoms involving the Temporomandibular Joint, the masticatory muscles and other associated structures. Intra/peri-articular injections of various products is a part of the minimally invasive treatments for TMD management. It offers a least-invasive option with affordable agents that are easy to obtain and could be applied in outpatient office setting. **Objective:** The aim of this study is to compare the effectiveness between peri/ intra-articular injections and conventional treatments in patients with TMD on pain management and TMJ's mobility. **Material and methods**: A comprehensive research in MEDLINE, SCOPUS and Cochrane Central Registry of Controlled Trials was conducted from January 2022 to April 2022. **Results**: 10 studies were included ranging from moderate to high methodological quality. Five RCT compared different conventional therapies between them, three analyzed the difference between various intra/peri-articular injection's products and two RCT compared conservative therapies to intra/peri-articular injection's treatment. **Conclusion:** Peri/intra-articular injections allowed a higher effect on mouth aperture based on maximal mouth opening or equivalent assessment tool. Both conventional and peri/intra-articular injections displayed an equivalent diminution regarding pain evaluation by visual analogue scale or numerical rating scale. Regarding the effectiveness of the therapies, the following classification was established, from the most to the least effective: combination of occlusal splint with intra-articular injection of PRP, Bethamethasone or Sodium Hyaluronate, followed by muscular exercise, manual therapy, intra-articular injection of HA and PRP, splint therapy, intra-articular injection of Lidocaine and Dextrose, TENS and Dry Needling.

KEYWORDS

Temporomandibular joint.

Temporomandibular disorders.

Conservative or Conventional therapy.

Minimally invasive treatment.

Peri/ Intra-articular injection.

Prolotherapy.

INTRODUCTION

1. Anatomy of Temporomandibular Joint Complex

The Temporomandibular joint (TMJ) is a ginglymoarthroidial synovial joint that connects the skull to the mandible base. TMJ is implied in both language and mastication. The optimal functioning of the TMJ depends on various factors in a complex equilibrium: the congruence of temporal and mandibular bony components, the articular disk, the capsule with both the ligaments and muscular components.

The superior part of the complex is made by the temporal bone: the roof of the joint is constituted by the mandibular fossa, the anterior border by the articular eminence, the posterior border by the postglenoid process, the medial border by the entoglenoid process and the lateral border by a crest connecting the articular eminence with the postglenoid process. The mandibular osseous component is a condylar process with a convex superior surface. The most frequently affected surface of the TMJ complex are the anterior and superior ones due to the slope of the preglenoid plane.[1]

The articular disk is the most important structure for the mobility of the TMJ complex and divides the joint into superior and inferior compartments. It's an oval and biconcave structure made of avascular fibrocartilaginous tissue. This complex joint is responsible of two functional movements: a rotary hinging movement in the inferior compartment and sliding movement in the superior one. In a sagittal plane, the normal position of the disk in closed mouth is a 12 o'clock position in which the posterior band is located on the condyle, near the vertical line. Normally, the junctions between the posterior band and the bilaminar zone (posterior disc attachment) is under 10° of the vertical line. If the angle between the 12 o'clock line and the junctions is superior to 10°, it's pathologic. In an open-mouth position, the junction between the anterior band and the intermediate zone is normally interposed between the condyle and the articular eminence.[2]

The joint is surrounding by several masticatory muscles that could be divided into adductors and abductors. The most important jaw closer's muscle is the masseter that come from the zygomatic arch and insert onto the angle and lateral surface of the ramus of the mandible. The second one is the medial pterygoid that has a parallel path to the masseter from the maxillary tuberosity to the medial surface of the mandibular ramus. The third one is the temporalis muscle running from the temporal fossa to the coronoid process of the mandible. The muscles responsible of jaw's opening are lateral pterygoid and digastric muscle. The lateral pterygoid could be divided in two parts: the superior one that goes from the infratemporal part of the greater wing of the sphenoid bone to the anterior part of the articular disk and the inferior one from the lateral part of the lateral pterygoid plate to the anterior surface of mandible's neck. The superior part allows coordination movement of disk and mandible. The lower part is mainly implicated in forward movement of the jaw, mouth opening and lateral deviation of the mandible to one side. If there is a contraction of the inferior part of both lateral pterygoid muscles (right and left), it moved the condyles forward out of the fossa onto the apex of both eminences. The digastric muscle is also made by two different bellies: the posterior one comes from the mastoid process and the anterior from the digastric fossa of the mandible. Both bellies joined to form a tendon, attached to the hyoid through a fibrous loop. Its contraction moves the mandible symphysis backwards producing a retrusive and opening movement of the mandible.[1]

The innervation of the TMJ is made by the auriculotemporal, deep masseteric and temporal branches of the mandibular nerve V3.

To open the jaw, the inferior surface of the disc rotates in the inferior joint compartment followed by a translation of the condyle and attached disc over the articular eminence in the superior joint compartment.[2]

2. Historical overview of Temporomandibular disorders

The first description of temporomandibular disorder (TMD) was in British surgeon's article in 1887 about surgical management of disc displacement. In 1934, Costen published an influential paper showing a link between dental malocclusion and ear symptoms such as otologic pain in the TMJ, tinnitus, impaired hearing, dizziness.[3,4] During the late 30s, the most common therapies for TMD were bite-raising appliances for mandibular dysfunction.[5] In the following decade, TMDs were diagnosed as TMJ pathology and researches focused on single factor explanations such as TMJ, muscle or dental occlusion with only few supporting evidences. [3,4] Through the 1950s, dental professionals investigated the consequences of occlusal interferences on the function of masticatory muscles, correlated by electromyographic studies.[3,5] In the 60s and 70s, occlusion and emotional stress were identified as the major causes of functional disorders of the masticatory disorders. In the 1970s, Farrah and McCarty described a link between intracapsular components and pain disorders.

Recently, TMDs have been described as a multifactorial complex disorder with comorbidities' overlapping of physical signs and symptoms and social interactions. In 1992, Research Diagnostic Criteria for temporomandibular disorders (RDC/TMD), the first evidence-based diagnostic method for TMD, was published and based on a biopsychosocial of pain with 2 assessment axes: physical and psychosocial. It remained a gold standard in the diagnosis of TMD for years. In 2014, a new classification was published: Diagnostic criteria for temporomandibular disorders (DC/TMD), based on the last one with some modifications.[3]

3. Signs and symptoms of Temporomandibular disorders

TMDs are defined as a group of related musculoskeletal conditions affecting 10-15% of adults and 4-7% of adolescents in both developed and developing countries.[6] TMD is a generic term to describe a group of disorders involving a series of clinical signs and symptoms affecting the temporomandibular joint, the

masticatory muscles and other associated structures. [5] The most common symptoms are pain, limited range of motion and TMJ sounds.[7] The pain is usually the main complaint and is located in the masticatory muscles and/or pre-auricular region that could be worsen by chewing or other jaw activity. It can be intermittent or persistent, usually of moderate intensity and increase by jaw function such as chewing, yawning or talking.[4] The chronic pain could lead to anxiety, depression, social impairment, physical disability and reduced working capacity. It exists a direct correlation between TMD and lower quality of life.[8] The patients could also describe joint clinking and parafunctional habits.[9] Other symptoms include joint noise, painless masticatory muscles hypertrophy, muscle fatigue, headache and bruxism.[6] The main clinical signs are pain and/or tenderness upon palpation of TMJ and masticatory muscles. The most common pain-related TMD are myalgia, arthralgia and headache.[4] A restriction of mouth movements with a limitation or an interference of the mandible in the opening are also reported. A normal neurological examination is usually detected.[6, 9]

4. Taxonomy of Temporomandibular disorders

Temporomandibular disorders are divided in 4 groups (*Annex 1*): temporomandibular joint disorders, masticatory muscle disorders, headache related to temporomandibular disorders and associated structures disorders.

Temporomandibular joint disorders are constituted by 5 subgroups: joint pain, joint disorders, joint diseases, fracture, congenital/ developmental disorders.

Joint pain could be divided in arthralgia which is a painful sensation located in TMJ during function or parafunctions and arthritis, an inflammatory or infectious process causing edema, erythema and/or increased temperature.[10]

There are 3 main types of joint disorders: disc displacement, hypomobility and hypermobility. Disc disorders is the most frequent conditions affecting the TMJ and is defined by an abnormal relationship between the disc and the condyle. The most common displacement is an anterior or anteromedial position of the

disc.[7] A disc displacement with reduction is characterized by the displacement or misalignment of the disc with the condyle when the mouth is closed and the return of its anatomical position during mouth opening. In opposite, a disc displacement without reduction is seen when the misalignment of the disk is maintained during the whole process of opening and closing the jaw, and usually associated with a limited opening.[1] Hypomobility of the TMJ could result from adhesions or fibrous/osseous ankylosis. Hypermobility disorders are due a displacement of the condyle out of the mandibular fossa, remaining in the joint capsule. A complete dislocation constitutes a luxation and a partial one a subluxation.

It exists various types of joint diseases: degenerative joint diseases, systemic arthritides, condylysis/idiopathic condylar resorption, osteochondritis dissecans, osteonecrosis, neoplasm and synovial chondromatosis.[10] Degenerative joint disease is the most common pathology affected TMJ and is subdivided in osteoarthrosis and osteoarthritis. Osteoarthrosis is an abnormal disc position or TMJ's unsuccessful adaptation of mechanical forces in case of disc displacement or disc interferences disorders. Osteoarthritis is a progressive degeneration of bone, cartilage and supporting tissue causing stiffness, pain and loss of function.[11]

Condyle fractures are common injuries and represent 25% of all mandible fracture. If it remains untreated, it could lead to an ankylosis of the TMJ.[1]

Congenital disorders include condylar aplasia, hyperplasia and hypoplasia.[10] Condylar aplasia is a rare condition in which a failed development of the mandibular condyle is detected. Condylar hypoplasia is un underdevelopment of the mandibular condyle whereas hyperplasia is an overgrowth of the mandibular neck and homolateral half of the mandible.[1]

Masticatory muscle disorders are made by 5 subgroups: muscle pain, contracture, hypertrophy, neoplasms, movement disorders and masticatory muscle attributed to systemic/central pain disorders.[10]

Headache related to TMD is located on the temple region and secondary to pain-related TMD. It's affected by jaw movement, jaw function or parafunction.[4]

Disorders related to associated structures are related to coronoid hyperplasia.[10] It's an acquired/ developmental enlargement or elongation of the mandible's coronoid process. It could lead to limitation of condylar translation and mouth opening's range.[1]

5. Diagnosis of Temporomandibular disorders

Adults looking for a TMD-pain diagnosis represented 3,9% and adolescents 4,6%.[4]

The most worldwide accepted diagnostic criteria was RDC/TMD which was revised and replaced by the DC/TMD in 2014. These diagnostic criteria are based on two axes: Axis I (physical) and Axis II (psychosocial).

Axis I allows a standardized method for the interpretation of signs and symptoms related to TMD. Through an anamnesis and an examination, the operator evaluates pain localization, jaw movements limitation in eccentric parameters and mouth opening, TMJ noises, mobility pain and pain upon palpation of the masticatory muscles and TMJ. The type of pain is determined by patient's description and its reproduction by the examiner through palpation and mouth's movements. Joint's disorders and degenerative diseases require joint's images to obtain a final diagnosis.

Myalgia and arthralgia are suspected when a patient described a pain in the jaw, temple, in or in front of ear modified with jaw movement, function or parafunction during the last 30 days. Myalgia is diagnosed if there is both a confirmation of pain location in the temporalis or masseter muscle and a reproduction by palpation of the incriminated muscle or maximum opening movements. Three types of myalgia have been differentiated: Local myalgia if the manipulation recreates pain in masseter or temporalis muscle, myofascial pain if it spreads beyond the site of palpation within the boundary of muscle, and myofascial pain with referral if it's beyond the site of palpation. Arthralgia often occurs jointly with a myalgia. It's defined as a pain located in the TMJ reproduced by palpation

of the lateral pole or TMJ's eccentric movements. Headache could also be described by TMD patients and requires a correct differential diagnosis. In TMD, the patient reports a headache in the temple in the last 30 days modified by jaw movement, function or parafunction. The palpation of the temporalis muscle or jaw's movements such as maximum opening, translation or protrusive movements should recreate the pain.[4]

Joint's disorders are assessed through the presence or absence of TMJ noises and jaw limitations. It allows a primary diagnosis of disc displacement with or without reduction.

A disc displacement with reduction is diagnosed when a patient described TMJ noises such as clicking, popping o snapping noise in the last 30 days or during the exam which are reproduced by the operator during opening and/or closing movements and translation or lateral movements. A distinction is made with disc displacement with reduction and intermittent locking if the patient reports an episode of jaw locks with limited mouth opening in the last 30 days. A description of jaw lock limited mouth opening or a limitation of jaw opening severe enough to limit jaw opening and interfere with the ability to eat is associated with disc displacement without reduction. A disc displacement without reduction with limited opening is distinguished when the interincisal distance is lower than 40mm during mouth opening. The only objective method to diagnose a joint disorder is a Magnet Resonance Imaging (MRI) and is necessary to establish the final diagnosis.

Joint diseases such as arthrosis or osteoarthrosis are detected through reports of crepitation in the last 30 days during jaw movements confirmed by examiner's palpation.[10] Computed tomography (CT) scans are used to confirm the final diagnosis.[4]

The second axis assess patient's psychosocial situation and pain consequences. It includes 5 simple self-reports screening instruments: Graded Chronic Pain Scale (GCPS) to evaluate pain intensity and pain-related disability, Pain drawing to localize the pain, Jaw Functional Limitation Scale Short-form (JFLS) to determine the limitation, Patient Health Questionaire-4 (PHQ-4) to detect

psychological distress due to anxiety or depression and Oral Behavioral Checklist (OBC) to evaluate parafunction. Widespread pain detected with pain drawing suggest the use of comprehensive instruments. The comprehensive evaluation of a patient follows the Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials (IMMPACT) recommendations. It comprises PHQ-9 for depression, Generalized-Anxiety Disorder (GAD-7) for anxiety, PHQ-15 for physical symptoms, Pain drawing and OBC.[12]

6. Treatment of Temporomandibular disorders

In the US, the estimated cost attributed of diagnosis and treatment of TMD is around $100 billion a year.[4]

There is a consensus regarding beneficiary of conservative and reversible therapies in painful TMD that should constitute the two first options of treatments.[6]

The first line of management is constituted by conservative treatments including patient's educations and self-management, medications, intraoral appliances, physiotherapy and low-level laser therapy. The second line is made of less-invasive treatments such as intra-articular injections (IAI), arthrocentesis with or without occlusal splints, arthroscopy alone or in combination with IAI. The last line corresponds to surgical treatments including minimally invasive arthroscopic procedures or invasive open joint surgeries.[13] Depending on each patient, a multimodal strategy may be included in the treatment plan.[12]

6.1. Conservative treatments

The education method provides an adapted explanation of the TMD's mechanisms, etiology and prognosis, allowing the patient to be conscient of a link between TMJ's parafunctions and psychosocial factors, and its consequence on musculoskeletal pain. The beneficial of patient's implication in TMD management has been proven.[7]

The self-management program consists of self-care techniques including therapeutic exercises, relaxation techniques such as diaphragmatic breathing, automassage of the masticatory muscles, advice about sleep and pain-free diet. The success of this program depends on patient's motivation, cooperation and compliance.[5,7,12] Therapeutic jaw exercises provide coordination training, relaxation and strengthening of muscles.[4]

The pharmacotherapy is used to alleviate TMD's manifestations. Non-steroidal anti-inflammatories (NSAID) medications are used in case of arthralgia, arthrosis or arthritis for its analgesics and anti-inflammatory effects. Cyclobenzaprine is commonly used in TMD muscle pain for its myorelaxant effect, as well as Tizadine, even if it shows lesser effect. Neuromodulating drugs such as tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, benzodiazepines, gabapentin and pregabalin as well as lidocaine patches are used in chronic TMD. Anxiety symptoms, sleep disturbance and headache related to TMD should also be considered in treatment selection.[7,12]

A psychological therapy is recommended in case of chronic TMD. Cognitive-behavioral therapies show signs of long-term improvement in TMD pain, depression and interferences with activities but must remain a part of a multimodal therapy.[9,12]

Oral appliance is one of the most common TMD treatment.[5] Orthodontic appliance is a removable acrylic resin appliance covering the teeth which constitutes a reversible and atraumatic approach. It's used to alter occlusal relationship, to prevent occlusal wear and teeth's mobility, to treat painful TMJ, to relieve jaw muscle pain and dysfunction. Stabilization appliances, also called bite guard or stabilization splint, cover all mandibular or maxillary teeth and are worn while sleeping in order to treat TMDs' symptoms, to reduce occlusal wear and manage unstable occlusion. The occlusal surface should be adjusted initially and regularly to adapt maxillomandibular relationship's modifications. In adjunction with other therapies, it could be a viable treatment option for internal TMJ disorder.[5] Intraoral appliances show also an effect on cognitive awareness.[7]

Manual therapies are a part of TMD management and allow various techniques. It includes joint manipulation targeting specific ligament, postural correction, myofascial therapy applied to masticatory muscles and mobilization of the cervical spine.[9]

Sensory simulation treatments such as transcutaneous electrical nerve stimulation (TENS) or acupuncture act on afferent nervous system in order to modulate endogenous pain control systems and reduce pain.[4] Acupuncture or dry needling is the insertion of monofilaments needles. It allows an immediate reduction of local, referred and widespread pain, restoration of range movement, improvement in range of motion, muscle activation patterns and an effect on immediate chemical environment of active myofascial trigger points.

Ultrasound could be used in adjunctions to other therapies to reduce the inflammation, relax masticatory muscles and increase the blood flow.

Low-level laser therapy (LLLT) constitutes a safe, non-pharmacological and affordable alternative in TMD management. It shows anti-inflammatory and analgesic effects. It also allows muscle relaxation and inactivation of myofascial trigger points.[7]

6.2. Minimally invasive treatments

Arthrocentesis is an intra-articular irrigation or lavage of the TMJ with or without corticosteroids. It could be used as a palliative treatment in patients with acute episodes of degenerative or rheumatoid arthritis. It allows improvement in mouth opening and pain reduction during mandibular movements.[5, 11]

Arthroscopy is a procedure done primarily to allow a direct observation and biopsy of the upper joint space in case of painful joint and hypomobility of a persistent non-reducing disc. It allows an increased in disc mobility.[5]

Injections of various products have been used to treat different types of TMD. Wet needling consists of intramuscular injections. It's made by hollow-bore

needles to transfer substances such as Botulinum toxin, corticosteroids, local anesthetics solutions, sclerosants or saline solutions.[14]

Botulinum toxin type A (BoNT-A) is the fermentation product of a gram-positive anaerobic bacteria called Clostridium botulinum. Its local injection inhibits the release of nociceptive mediators such as substance-P, glutamate and the peptide related to calcitonin gene. It's used to manage different types of pain such as TMD, neuralgia and secondary headache. BoNT-A has also been used in the management of chronic recurrent dislocation of the TMJ, based on the theory of the contribution of lateral pterygoid muscle in the dislocation.[7, 15]

Dextrose is a proliferative agent that produces a low-grade inflammatory response in the tissues favoring repair and regeneration of the tissue. It could be used in the management recurrent temporomandibular joint dislocation.[15]

Hyaluronic Acid (HA) is a high-molecular-weight glycosaminoglycan naturally present in extracellular matrix of TMJ which provides viscoelastic properties to the joint, reduce inflammation and pain. Intra-articular injection of HA is used to stimulate its natural production, reduce fibrous tissue proliferation and inhibit osteoarthritis progression. It could be used in intra-articular single or multiple injections or associated with other procedures such as arthrocentesis or arthroscopy.[5, 11]

Platelet Rich Plasma (PRP) are obtained by the centrifugation and separation of platelets of autologous blood which are then diluted in saline solution to obtain the correct concentration. It stimulates cell proliferation and production of cartilage matrix by chondrocytes and bone-narrow derived mesenchymal stroma cells. It also increases the production of HA by synoviocytes. It could be used as intra-articular injections and in combination with arthroscopy or arthrocentesis.[11]

6.3. Surgical treatments

TMD surgical treatments are complex procedures with latent complications. Their use should be limited to painful TMD in which conservative and minimally invasive treatments do not provide sufficient effect.

Arthrotomy is a TMJ's open surgical intervention used in case of fibrous or osseous ankylosis, neoplasia, severe chronic dislocation and severe osteoarthritis. Discoplasty and disc repositioning with plication allow a reduction of jaw pain and noise as well an increase in mouth opening.[5]

Capsulorrhaphy could be done in case of recurrent temporomandibular joint disjunction using an arthrotomy approach or an arthroscopic technique to tighten or strengthen of the TMJ capsule and ligaments. The arthroscopic approach constitutes a minimally invasive surgical technique that may involve the use of sclerotic agents, laser and/or electrocautery.[15]

RATIONALE, OBJECTIVES AND HYPOTHESIS

1. Rationale

The injection of certain substances in the management of TMD offers a least-invasive option with affordable agents that are easy to obtain and could be applied in outpatient office setting. Various agents could be injected to manage muscular or arthrogenous TMD. It is a new type of treatments using off-label products.

Various RCTs have been designed to compare the injection of products with conservative therapies and minimally invasive therapies but there is not a clear analysis of the most effective procedures and agents in the different types of TMD.

Systematic reviews have been commonly used to classify the efficacity of different treatment options. Thus, investigation of the efficacy of injectable techniques by this strict scientific design may provide strong and abundant evidence in the management of TMD.

2. Objectives

The aim of this study is to compare the effectiveness between peri/ intra-articular injections and conventional treatments in patients with TMD on pain management and TMJ's mobility.

The specific objectives are:

- Compare results of treatments with peri/ intra-articular injections and conventional methods regarding maximal mouth opening or equivalent assessment tool.
- Compare results of treatments with peri/ intra-articular injections and conventional methods regarding pain evaluation by visual analogue scale or numerical rating scale.

- Make a classification of the most effective conservative and minimally invasive treatment in pain management and TMJ mobility for patients with TMJ disorders presenting pain and limited mouth opening.

3. Hypothesis

Peri/ intra-articular injections show a higher effect on pain management and TMJ's mobility compared to conventional treatments in patients with TMD.

MATERIAL AND METHODS

1. Protocol

This systematic review was realized based on the Preferred reporting Items for the PRISMA Extension Statement for reporting of Systematic Reviews Incorporating Network Meta-Analyses of Health Care Interventions (PRISMA-P checklist).[16]

2. Search strategy

All pertinent Randomized Controlled Trials (RCTs) in English were screened by comprehensive research in MEDLINE, SCOPUS and Cochrane Central Registry of Controlled Trials from January 2022 to April 2022.

The following key words were used: Temporomandibular joint; TMJ; temporomandibular disorders; TMD; conservative therapy; Dry needle; acupuncture; Pharmacotherapy; Manual therapy; physiotherapy; oral appliance; Splint; TENS; injection; wet needling; Botulinum Toxin; Dextrose; hyaluronic Acid; Platelet Rich Plasma; Corticosteroid; Randomized Controlled trials; RCT.

The following Boolean words were used between keywords: OR; AND.

The exact keywords are described in the following table (Table 1) and in *Annex 2*.

Table 1: Research description by Database

DATABASE	SEARCH	FILTERS	DATE
MEDLINE	((Temporomandibular joint OR TMJ) OR (temporomandibular disorders OR TMD) AND ((conservative therapy) OR (Dry needle OR acupuncture) OR Pharmacotherapy OR ((Manual therapy) OR physiotherapy) OR ((oral appliance) OR Splint) OR TENS) OR ((injection) OR (wet needling) OR (Botulinum Toxin) OR Dextrose OR (hyaluronic Acid) OR (Platelet Rich Plasma) OR Corticosteroid)	○ Randomized Controlled Trial, ○ in the last 5 years, ○ Humans, ○ English, ○ MEDLINE.	25/02/2022
SCOPUS	((Randomized Controlled trial) OR RCT) AND (((Temporomandibular joint OR TMJ) OR (temporomandibular disorders OR TMD) AND ((conservative therapy) OR (Dry needle OR acupuncture) OR Pharmacotherapy OR ((Manual therapy) OR physiotherapy) OR ((oral appliance) OR Splint) OR TENS) OR ((injection) OR (wet needling) OR (Botulinum Toxin)	○ From 2017 to 2022. ○ English. ○ Articles. ○ Exact keywords: ▪ “Human”. ▪ “Humans”. ▪ "Randomized Controlled Trial". ▪ "Pain Measurement".	25/02/2022

	OR Dextrose OR (hyaluronic Acid) OR (Platelet Rich Plasma) OR Corticosteroid))	▪ "Visual Analog Scale". ▪ "Pain Intensity". ▪ "Quality Of Life". ▪ "Range Of Motion, Articular". ▪ "Range Of Motion". ▪ "Pain Threshold" ▪ "Mouth Opening".	
COCHRANE	((Temporomandibular joint OR TMJ) OR (temporomandibular disorders OR TMD) AND ((conservative therapy) OR (Dry needle OR acupuncture) OR Pharmacotherapy OR ((Manual therapy) OR physiotherapy) OR ((oral appliance) OR Splint) OR TENS) OR ((injection) OR (wet needling) OR (Botulinum Toxin) OR Dextrose OR (hyaluronic Acid) OR (Platelet Rich Plasma) OR Corticosteroid)	○ Years first published: From 2017 to 2022.	25/02/2022

3. Selection criteria

The following inclusion criteria were based on the PICOTS process:

- (P) Patients: Patients with arthrogenous or muscular TMD based on the RDC/TMD or DC/TMD protocol or clear diagnosis with signs and symptoms of TMD.
- (I): Peri/Intra-articular injection's treatment 1) HA intra-articular injections; 2) Corticosteroid intra-articular injections; 3) BoNT-A injection; 4) PRP injections; 5) Dextrose injections.
- (C) Comparator: Conservative therapy 1) Muscular exercise; 2) Manual therapy 3) Intra-oral appliance (orthodontic appliance and stabilization splint); 4) Dry Needle techniques; 5) TENS.
- (O) Outcomes: The first outcome is a decreased in pain intensity scores using a visual analogue scale (VAS) and a numerical pain rating scale. The second outcome is an improvement in mouth opening using interincisal measurement.
- (T): short time (≤ 5 months) and intermediate time (≥ 6 months to 4 years).
- (S) Study design: RCTs of the last five years containing the outcomes of interest and the comparator.

4. Exclusion criteria

The following exclusion criteria were applied: 1) RCTs comparing one of the outcomes with surgical treatments. 2) RCTs in which the injections products are used in adjunction of arthroscopy or arthrocentesis. 3) Headaches not associated with arthrogenous or muscular TMD. 4) Bruxism not clearly identified as a TMD symptom. 5) Full-text not in English. 6) Unclear outcomes.

5. Data extraction

A data extraction was made by an operator. The extraction form was later revised by another reviewer. The extracted data are RCTs characteristics including author, study design, subgroups, diagnostic criteria used, age of patients, male-female ratio, interventions, duration of treatment/frequency and outcomes measures. Two tables were created: one about RCT characteristics and the other about subgroups, interventions, follow-up frequency and outcomes results. The absence of a data was expressed as “NC” in the table. About age of patients, the mean age or range was quoted and the male-female ratio was expressed in percent. Among the outcomes results, only the statistically significant results or main results were reported.

5.1 First outcome assessment: Pain evaluation

5.1.1. Visual Analogue Scale (VAS)

The VAS for pain allows a unidimensional evaluation of pain with a continuous scale of 10cm with one extreme counting for 0 (“no pain) and the other to 100 (“worst imaginable pain”). It’s free scale in the public domain. The patient places a perpendicular line to the VAS line at the point reflecting their pain intensity.

5.1.2. Numeric rating scale (NRS)

The NRS is a segmented numeric version of the VAS in which the patient should select on the scale a number between 0 (“no pain) to 10 (“unsupportable pain”) regarding the pain intensity.[17]

5.2 Second outcome assessment: Maximum mouth opening (MMO)

MMO or Maximal interincisal opening is the distance expressed in millimeters between superior and inferior incisal edges when the patient opens the mouth as widely as possible, using a ruler.[18] Being 40 mm the normal MMO average.

6. Quality assessment

Critical Appraisal Skills Program (CASP) Randomized Controlled Trial Standard Checklist[19] was used to assess the methodological quality of each article. The following 11 criteria are evaluating: clearly focused question; randomized; same number of patients at the beginning and end of the study;

participants, investigators and people analyzing are blinding; study group similar at the beginning; same level of care for each group; effects comprehensively reported; reports of the estimate of the intervention or treatment effect; the benefits of RCT outweigh the harms and costs; results applicable to our population/ dental clinic; provide greater value to the people in the care than any of existing interventions. Each criterion could be answered with a “Yes” or “+”, a “No” or “-“ and a “Can’t tell” or “?”. A score between 0 to 11 could be obtained, with a maximum of 11.

RESULTS

1. Trial selection

The electronic search on the 3 databases resulted in 706 published references. After removing all the duplicate, only 465 references remained. After screening the tittles, 44 abstracts were analyzed. Among them, 27 were excluded for the following reasons: unclear diagnosis of TMD (n=2), not evaluation of both pain and mouth opening (n=19), comparison with non-included types of treatments (n=5). 17 full-text articles were screened and 7 were excluded for the following reasons: not in English (n=1), not RCT (n=2), unclear outcomes (n=2), comparison with non-included types of treatments (n=1). Ten references were included (*Annex 3*) in this systematic review: all the articles were RCT.[20-29]

2. Trial characteristics

The characteristics of the ten included studies are listed in table 4 (*Annex 5*). Among ten RCT, three were single-blinded[20, 25, 27], four were double-blinded [22, 23, 24, 29], two were also multicenter[20, 22] and one was also prospective[20].

The total number of participants ranged from 24[25] to 120[20]. All the participants were adults. The age of the including patients ranged from 18 to 65 years with mean ages from 28.35[23] to 47[24] years old. The male/female ratio showed a higher percentage of women in all studies with a ratio ranging from 14/86%[24] to 45.63/ 54.37%[20].

Five studies[22, 24, 26, 28, 29] used the RDC/TMD diagnostic criteria to evaluate the presence of TMD: two[24, 29] of them included patients presenting RDC/TMD I, II and III, one[24] only patients with RDC/TMD I and another one[22] patients with RDC/TMD associated to tinnitus. To identify TMD, three studies[20,21,27] applied the DC/TMD diagnostic criteria: two[21,27] of them included only TMJ arthralgia and the other one[20] all types of TMD. Two[22, 29] trials used MRI with Wilkes classification to confirm TMD's diagnosis.

Six[20, 21, 23, 25, 26, 28] studies evaluated pain through a visual analogue scale and the other four studies via a numerical rating scale[22, 24, 27, 29]. Mouth opening was evaluated through Maximum mouth opening in seven studies[20, 21, 23, 25, 26, 28, 29], Mandibular range of motion in one[22], maximum interincisal opening[24] in another one and Total opening distance in the last one[27].

3. Conservative and minimally invasive therapies

Among the conservative therapies, three studies[20, 21, 23] used occlusal splints, two trials[26, 24] applied TENS, three studies[20, 22, 26] provided exercise therapy program and education for self-management, one trial[22] applied cervico-mandibular manual therapy and another one[28] dry needling.

Out of the injection therapies, three[23, 24, 29] trials used an intra-articular combination of lidocaine and dextrose, two[24, 29] applied only lidocaine, one[21] provided a preauricular injection of Sodium hyaluronate or betamethasone or PRP, another one[25] applied an intraarticular of HA alone or in combination with PRP.

One[27] of this study analyzed the immediate effect of intervention and the others[20, 21, 22, 23, 24, 24, 26, 28, 29] performed a longer follow-up, up to 1 year.

4. Effects on pain

One trial[27] showed a significant immediate reduction of pain after the application of TENS. Another study[26] demonstrated a significant decrease of pain between each session for both TENS and muscular exercise groups. In comparison with a control group receiving educational counselling, the other groups submitted to muscle energy technique, occlusal splint therapy or combined treatment, showed a significant reduction of pain after 3 months and no significant difference between them.[20] In another trial[22], the group submitted to the combination of exercise, education and manual therapy, showed a

greater reduction of pain than those receiving exercise/education alone. The application of superficial or deep dry needling technique showed a reduction of pain at trigger palpation points after 3 and 6 weeks.[28]

Compared to a control group with bite splint, there was a significant pain reduction in the groups providing a combination of bite splint and peri-auricular injection of betamethasone, sodium hyaluronate or PRP, with a higher reduction in the bite splint and PRP group.[21] In another study, the combination of anterior bite splint and prolotherapy showed a significant reduction of pain after 1 year in comparison to the use of anterior bite plane alone.[23]

In one trial[24], there was not a significant difference at 3 months between intra-articular injection of lidocaine alone, or in combination with dextrose. However, the last group showed a more frequent increase at least of 50% of pain improvement than the control group. Another study[29] demonstrated a higher reduction of pain after 3 months with injection of a combination of dextrose and lidocaine rather than lidocaine alone.
Intra-articular injection of HA alone or in combination with PRP showed a significant pain reduction at 1-month follow-up. However, lidocaine alone provided a significant increase of pain between 3 to 6 months.[24]

5. Effects on Mouth opening

One study[26] demonstrated a significant improvement of MMO between each session for home exercise and TENS groups and no significant difference between both groups. Another trial[27] showed no immediate significant improvement of total oral distance after TENS application. As compared to educational or bite splint groups, there was a highly significant improvement after 3 months of maximum mouth opening for muscle energy technique group and combined group.[20] In another trial[22], the group submitted to the combination of exercise, education and manual therapy, showed a higher increase of mandibular range of motion than those receiving exercise/education alone.

In one trial, there was a significant improvement after 6 months of pain-free mouth opening in bite splint, combination of bite with betamethasone or sodium hyaluronate or PRP groups. The bite splint group showed a smaller average rate per week and the combination of bite splint and PRP group had a larger average rate per week.[21] In another study, the combination of anterior bite splint and prolotherapy showed improvement of mouth opening after 1 year in comparison to the use of anterior bite plane alone.[23]

In one trial[24], there was a substantial improvement of MIO at 3 months for both intra-articular injection of lidocaine alone and in combination with dextrose. Another study[29] demonstrated a higher improvement of MIO after 3 months with injection of a combination of dextrose and lidocaine rather than lidocaine alone. Intra-articular injection of HA alone or in combination with PRP showed a significant increase of MMO after 2 weeks. However, lidocaine alone was submitted to a significant decrease of MMO between 1 and 3 months.[24]

6. Quality assessment

Quality scores (*Annex 4*) of the including studies ranged from 7[25] to 10[22,24] out of 11. Quality assessment identified that all the studies were randomized clinical trials with a clearly focused question, well-defined inclusion and exclusion criteria. As the studies were all on humans with TMD, the results were all applicable to our population and provided a greater value in comparison to other any interventions, as they showed efficacy on their target population.[20-29]

Almost all study provided the same level of care for each group with the exception of one[28] that included a group of healthy patients without treatment. Four studies [22, 23, 24, 29] were double-blinded, three were single-blinded[20, 25, 27] and for the other ones[21, 26, 28] it was unclear. Among the ten articles, four[20, 22, 24, 29] showed a loss of patients between the start and the end of their study from 2 to 13 participants' drop out. For three others studies, it was unclear[21, 25, 26]. Three trials presented differences between groups at the start of their study: one[23] was a difference in mean age and gender ratio, another one[25] was a difference in means values of

pain, joint sound and functional limitation and for the last one[29], it was a difference of gender ratio, pain duration and MIO. The confidence interval used to evaluate the effect of intervention was absent in half of the trials[23, 23, 26, 27, 29].

DISCUSSION

In this systematic review, five RCT[20, 22, 26, 27, 28] compared different conventional therapies between them, three RCT[24, 25, 29] analyze the difference between various intra/peri-articular injection's products and two RCT[21, 23] compared conservative therapies to intra/peri-articular injection's treatment. Regarding CASP Selective criteria, the including RCTs ranged from moderate (score 6-9) to high (score 9-11) methodological quality. The aim of this study was to compare the effectiveness between conventional treatments and peri/ intra-articular injections in patients with TMD on pain management and TMJ's mobility.

1. Conservative therapies

Two studies[26,27] showed the efficacy of TENS on TMD's pain and one[26] demonstrated a significant improvement of maximal mouth opening between each session. TENS application's protocol was different between both studies regarding their protocol, duration of session and especially duration of treatment with one study[26] giving one session by week for 4 weeks and another one[27] giving five successive sessions separated by 10 minutes of rest on the same day. This last RCT showed a simultaneously improvement of pain and a delayed improvement of jaw function with an enhancement only seen on the 5th session, that could explain the difference of results between these two studies. Furthermore, inclusion criteria varied between these two studies: one[26] of them used the RDC/TMD diagnosis criteria including both arthrogenous and myogenous TMD whereas the other one[27] used DC/TMD arthralgia subclass targeting specifically patients presenting TMJ disc displacement without reduction. Fertout et al[30] showed in their systematic review that TENS was effective on both arthrogenous and/or muscular TMD even if specific indications should be determined. They also demonstrated that TENS constitutes an effective non-drug based conservative therapy's option in the management of TMD improving pain and amplitude of mouth opening. One of the present

RCT[26] showed a significant higher pain improvement for TENS therapy in comparison to home exercise program. Therapeutic exercises stimulate the parasympathetic activity in order to increase blood flow and to obtain an analgesic effect based on the activation of a pain-gate mechanism.[31] Whereas TENS application is based on several interrelated theories: the gate-control theory, the endogenous release of morphine-like substance after electrical stimulation and the automatic and involuntary contraction of muscles.[32]

Two studies[20, 22] revealed the efficacy of manual techniques on pain and jaw aperture in TMD patients. A study including TMD patients with tinnitus showed that a combination of exercise, education and cervico-mandibular therapy has a significant effect on pain and maximum mouth opening in comparison to a combination of only exercise and education. Both manual therapy and therapeutic exercise have a neurophysiological effect within the central nervous system. A multimodal therapy allows a multidimensional effect on TMD patients. An osteopathic muscular energy technique alone or in combination with an occlusal splint showed a higher efficacy in comparison to a combination of education and counseling. Muscular energy technique acts on Golgi tendon receptor by stretching muscle fibers that inhibits muscle tension and leads to relaxation.[22] Occlusal splint therapy presented a similar effect on pain than muscular energy technique or the combinations of both and a lower effect on maximal mouth opening.[20] Splint allows a relaxation of masticatory muscles and a condyle centric relation reducing joint's overloading and favoring a normalization of blood supply. In this RCT all the types of TMD were including regading DC/TMD.[22] Zhang[33] et al. found different results and recommended in their systematic review occlusal splint as an election treatment for TMD patients with signs and symptoms of mandibular restrictions whereas in patients with TMD-related pain a combination of education, occlusal splint and manual therapy was suggested.

One RCT demonstrated that dry needling allowed an improvement in TMD-related pain but had no significant effect on maximum mouth opening. The authors recommended a multimodal approach when applying dry needling with the additional used of jaw exercises or other physical therapies such as

low-intensity laser or ultrasound.[28] Dry needling is based on intramuscular stimulation and mechanical disruptions of muscle fibers and nerve endings, as well as a reduction of the electrical activity. It doesn't require the injection of substances.[34]

2. Conservative and injections therapies

Two studies[21, 23] found that the combination of occlusal splint with intra/peri-articular injection has a better efficacy on pain and mouth opening in TMD patients than occlusal splint alone.

The combination of prolotherapy and occlusal splint showed a long-term relief of TMD symptoms and has been recommended as a therapeutic option in the management of TMJ's internal derangement. The prolotherapy solution was composed of 0.75mL of dextrose 50%, 1.5ml Lignocaine 2% with adrenaline and 0.75mL of bacteriostatic water. The solution was then injected in three sites: the posterior joint space, the anterior disc attachment to the lateral pterygoid muscle and the masseter attachment.[23] Even, if prolotherapy has proved is efficacity in other joints such as knee, it's a relatively new method in the management of TMD. The effect of dextrose prolotherapy is based on inflammatory and non-inflammatory process regarding the concentration of dextrose. A dextrose solution superior to 10% acts as an osmotic shock agent by dehydrating cells at the injection site leading to the release of cytokines and the increase of growth factor activity. This mechanism allows the deposit of new cells and tissue matrix in the joint with tissue maturation between six to eight weeks.[35]

The combined application of bite splint with hyaluronate acid showed similar effects than the combination of bite splint with betamethasone. The injection of these pharmacological products was realized in the preauricular area. Both of these substances present a potent anti-inflammatory effect on synovial tissue allowing a reduction of effusion and pain, and an increased range of motion on synovial joint. [21] Corticosteroids such as betamethasone could be used as

an intra-articular injection or an intramuscular injection. They are strong anti-inflammatory substances acting through various mechanisms such as decrease in the production of pro-inflammatory prostaglandin and leukotriene and a reduction in the number and activity of proinflammatory cells including lymphocytes, eosinophils, basophils and macrophages. HA plays an important role in joint lubrication and shows buffering, nutrition, anti-inflammatory and cartilage repair properties.[36]

It was also demonstrated that the application of PRP and occlusal splint led to a better effect on both pain and mouth aperture in TMD patients after 6 months.[21] PRP mechanisms are still under investigation but it seems to provide an anti-inflammatory, analgesic and chondrogenic effect in the joint.[37]

Even if these studies used different injection products at different targeted sites, they both found that the combination of an occlusal bite splint with intra-articular injections of anti-inflammatory and/or analgesic products allow better results than occlusal splint alone, one of the most widely used treatment of TMD.

3. Injections therapies

Three RCT[24, 25, 29] revealed the efficacy of intra-articular injections in the management of TMD regarding pain and mouth opening.

A study demonstrated that both injections of HA alone or in combination with PRP lead to a significant improvement of pain and jaw opening in TMD patients. However, the combination of the two products is the only one offering long-term better results. Injections were made in the upper joint with a solution of 1ml of HA or 0.5mL of HA and 0.5mL of PRP. [29] Viscosuplementation with HA provides tissue lubrication, nutrition and analgesic effect. It also promotes the release of adhesion area between the disc and mandibular fossa favoring joint mobility.[38] In combination with PRP's properties, it constitutes a minimally invasive option in TMD management that doesn't require surgical incision or tissue dissections.

Two studies[24, 29] showed a higher efficacy for a combination of dextrose and lidocaine injections than lidocaine alone. The protocol of injection was similar in these two studies as they both injected dextrose 20% alone or with Lidocaine 0.2% using the reference point at 1cm below the apex of the zygomatic arch. Sit et al.[39] recommended the application of dextrose injection in patient with internal derangement of TMJ that are refractory to conventional therapy as it constitutes an appropriate minimally invasive treatment.

4. Conservative Vs Injections therapy

a) Comparison of effects on pain

In case of myogenous TMD, dry needling allowed a significant reduction of pain.[28]

In the management of arthrogenous TMD, both conservative therapies and peri/intra-articular injections provided pain improvement. Among the conservative therapies, exercise, education and cervico-mandibular manual therapy showed their efficacy. The combination of exercise, education and cervico-mandibular manual therapy had better results than exercise and education alone.[22] Two studies[21, 23] revealed that bite spline, one of the most used conventional treatment, is less efficient alone than in combination with intra-articular injection of PRP or HA or Betamethasone. Out of the injections' therapies, intra-articular injection of HA or in combination with PRP reduced significantly TMD-related pain, even if only the combination of HA and PRP provided a long-term effect.[25]

Regarding mixed TMD, both conservative therapies and peri/intra-articular injections reduced significantly TMD-related pain. Various conventional therapies showed their efficacity: TENS, home exercise, occlusal splint, muscular energy therapy and a combination of occlusal splint and muscular energy technique.[20, 26] Occlusal splint, muscular energy therapy and a combination of both showed better results than education and

counseling.[20] TENS and home exercise provided similar results.[26] In two studies[24, 29] lidocaine alone or in combination with dextrose reduced pain but the combination with dextrose had significant better results.

b) Comparison of effects on maximal mouth opening

In one RCT about myogenous TMD, dry needling didn't have a significant impact on maximal mouth opening. That's why the authors recommended the addition of other therapies.[28]

In the management of arthrogenous TMD, both conservative therapies and peri/intra-articular injections provided mouth opening improvement. Among the conservative therapies, exercise, education, cervico-mandibular manual therapy and occlusal splint showed their immediate efficacy on jaw aperture whereas TENS had a delayed one.[21, 22, 23, 27] The combination of exercise, education and cervico-mandibular manual therapy had better results than exercise and education alone.[22] TENS therapy showed a significant effect on maximum mouth opening only after the 5th application.[27] Two studies[21, 23] revealed that bite spline, is less efficient alone than in combination with intra-articular injection of PRP or HA or Betamethasone. Out of the injections' therapies, intra-articular injection of HA or in combination with PRP reduced significantly TMD-related pain, even if only the combination of HA and PRP provided a long-term effect.[25]

Regarding mixed TMD, both conservative therapies and peri/intra-articular injections reduced significantly TMD-related pain. Various conventional therapies showed their efficacity: TENS, home exercise, occlusal splint, muscular energy therapy and a combination of occlusal splint and muscular energy technique.[20, 26] Muscular energy therapy and a combination of both showed better results than occlusal splint, education and counseling.[20] TENS and home exercise provided similar results.[26] In two studies[24, 29] lidocaine alone or in combination with dextrose allowed an improvement of mouth opening. However, only one[24] showed similar results between these two injection

solutions whereas the other one[29] found that the combination of dextrose with lidocaine had better results than lidocaine alone.

c) Classifications of conservative and injections therapeutic options for TMD management

The first intervention for TMD management should be based on education and home exercise as these are non-invasive methods that can quickly be set up. Patients should be informed of the meaning of their diagnosis. They should learn how to identify, monitor and avoid parafunctional habits such as daytime clenching, clicking or grinding teeth. They should be advised to adopt good sleep habits, to do deep breathing exercises and to apply moist heat to the area of discomfort for 10 min each day.[20,22] Home exercise should be realized by the patients twice a day. It must include active and passive jaw opening and closing exercises, isometric exercises, jaw stretching exercises and resistive jaw exercises. Instructions for resting jaw positions, head/neck and posture should also be given.[22, 26]

Then, the management should be based on TMD types as well as signs and symptoms.

Myogenous TMD patients with pain could be treated with dry needling. However, if patients show mouth opening limitations too, other types of conservative therapies should be added.[28] According to Machado et al.[34], several substances injections could also be considered in case of myogenous TMD-related pain such as local anesthetics and corticosteroids.

In case of arthrogenous TMD, various therapies could be implemented regarding patients' preferences, intensity and duration of their signs and symptoms. For patients with arthrogenous TMD-related pain and mouth-opening limitation, bite splint, cervico-mandibular manual therapy, TENS and intra-articular injections could be proposed.[21, 22, 23, 25, 27] If there is a marked limitation of jaw aperture, TENS should not be suggested or only in addition to

other therapy as it provides a delayed effect on jaw opening.[27] For persistent or intense pain, it should be recommended to use a multimodal therapy with a combination of a bite splint and injections products such as corticosteroid, HA, dextrose or PRP.[21, 23, 25] Out of the injection product, PRP seems to be the one providing a better and longer effect.[21, 25]

Mixed TMD includes both arthrogenous and myogenous etiology. Its management should involve various conservative and intra-articular injection therapy options. Occlusal splint, Muscular energy therapy, TENS, prolotherapy and lidocaine's injection could be suggested. As for arthrogenous and myogenous TMD's management, the election of the treatment should be based on patient's preferences as well as signs and symptoms. In case of TMD-related pain, TENS, manual therapy, occlusal splint and prolotherapy should be recommended.[20, 24, 26, 29] Prolotherapy seems to constitute a good option for a long-term management.[24] In case of mouth opening's dysfunction, TENS, manual therapy, injection of lidocaine or prolotherapy showed also good results.[20, 24, 26, 29]

Lee et al.[40] suggested in their systematic review an evidence-based algorithm for the management of TMD to simplify the decision-making process. After the diagnosis of TMD, the first line treatment should be conservative therapies including patient education and behavior modifications, soft diet, mandibular relaxation exercise and pharmacotherapy. In case of no improvement after two to three weeks, the management should depend on TMD types. If it's a myogenous TMD, alternative therapies such as physical therapies, acupuncture, dry needling, trigger point injections, splint therapy, electrical stimulation and botox injections should be considered. For an arthrougenous TMD, the diagnosis should be confirmed with an MRI. In this case, maxillomandibular appliances, physical therapies and intra-articular injections are recommended. If after two to three weeks, there still not have improvement, surgery should be considered.

5. Limitations

a) Limitations at review level

This systematic review only included studies in English which may lead to publication bias. Furthermore, it excluded arthrocentesis and arthroscopy studied in combination with injection, as it was chosen to focus only of the intra/peri-articular injections among the minimally invasive therapies.

b) Limitations at study level

All included studies were RCTs with acceptable methodological quality. However, the critical analyze of the evidence showed that the selected studies had different diagnosis criteria for TMD. Three studies[20, 21, 27] used DC/TMD, five[22, 24, 26, 28, 29] RDC/TMD, and two[23, 25] Wilkes classification. Furthermore, different types of TMD patients were included. Half of the studies[21, 22, 23, 25, 27] were focused on arthrogenous TMD, one[28] on myogenous TMD and four[20, 24, 26, 29] on both arthrogenous and myogenous TMD. The diagnostic heterogeneity made it difficult to compare studies between them.

Furthermore, various others limitations of varying degree were fund in the included studies. Six studies[23, 24, 26, 27, 28, 29] reported small sample size and recommended larger ones. Only one study[28] among the ten included had a control group without any interventions. Short follow-up period was also expressed in various RCT[23, 26, 28].

6. Recommendations

Within the above-mentioned limitations, some recommendation for clinical practice can be drawn. When a diagnosis of TMD is made, the management should start immediately with education and home exercise. TMD's type as well as intensity and duration of signs and symptoms should help the clinicians to determine the most appropriate treatment plan. TMD is a multifactorial

disease that may require multimodal therapy. Conservative and intra/peri-articular injection could be used alone or in combination depending on each case.

Further studies are recommended and should include: 1) high methodological quality RCT 2) with larger sample size; 3) long-term follow-up; 4) arthrogenous or myogenous TMD based on the same criteria; 5) direct comparison of conservative and peri/intra-articular injections therapies; 6) a control group without any intervention.

CONCLUSION

TMD is a multifactorial condition coursing usually with pain and/or mouth opening limitations. It includes different types of disorders such as temporomandibular joint disorders, masticatory muscle disorders, headache related to temporomandibular disorders and associated structures disorders.

The aim of this systematic review was to compare the effectiveness between peri/ intra-articular injections and conventional treatments in patients with TMD on pain management and TMJ's mobility.

- Both conservative and intra-articular injections therapies showed a significant improvement of maximal mouth opening in TMD patients. However, peri/intra-articular injections allowed a higher effect on mouth aperture based on maximal mouth opening or equivalent assessment tool.
- Both conventional and peri/intra-articular injections showed a significant pain reduction among TMD patients, displaying an equivalent diminution regarding pain evaluation by visual analogue scale or numerical rating scale.
- Based on pain scale and maximal mouth opening or equivalent assessment tool, the most effective therapy for the management of TMD patients with pain and limited mouth opening is the combination of splint with intra-articular injection of PRP, Bethamethasone or Sodium Hyaluronate. The second and third most effective options are formed by conservative therapies: muscular exercise and manual therapy. The fourth most effective is made by the intra-articular injection of HA and PRP, followed by splint therapy and intra-articular injection of lidocaine and dextrose. The least effective ones are constituted by TENS and Dry needling.

When considering all different options, it's important to take into account TMD types as well as intensity and duration of signs and symptoms to adapt patient's treatment plan.

Further investigations are required to establish precise indications of an early application of intra/peri-articular injection in TMD patients.

BIBLIOGRAPHY

1. Salamon NM, Casselman JW. Temporomandibular Joint Disorders: A Pictorial Review. Semin in Musculoskelet Radiol. 2020 Oct;24(05):591–607.
2. Whyte A, Boeddinghaus R, Bartley A, Vijeyaendra R. Imaging of the temporomandibular joint. Clin radiol. 2021;76(1):76.e21-76.e35.
3. Ohrbach R, Dworkin SF. The Evolution of TMD Diagnosis. J Dent Res. 2016 Sep;95(10):1093–101.
4. List T, Jensen RH. Temporomandibular disorders: Old ideas and new concepts. Cephalalgia. 2017 Jun;37(7):692–704.
5. Chang CL, Wang DH, Yang MC, Hsu WE, Hsu ML. Functional disorders of the temporomandibular joints: Internal derangement of the temporomandibular joint. Kaohsiung J Med Sci. 2018 Apr;34(4):223–30.
6. Ohrbach R, Dworkin SF. AAPT Diagnostic Criteria for Chronic Painful Temporomandibular Disorders. J Pain. 2019 Nov;20(11):1276–92.
7. Fernandes G, Gonçalves DAG, Conti P. Musculoskeletal Disorders. Dent Clin Nor Am. 2018 Oct;62(4):553–64.
8. Bitiniene D, Zamaliauskiene R, Kubilius R, Leketas M, Gailius T, Smirnovaite K. Quality of life in patients with temporomandibular disorders. A systematic review. Stomatologija. 2018;20(1):3–9.
9. Fernandez-de-las-Penas C, Svensson P. Myofascial Temporomandibular Disorder. Curr Rheumatol Rev. 2016 Mar;12(1):40–54.
10. Schiffman E, Ohrbach R. Executive summary of the Diagnostic Criteria for Temporomandibular Disorders for clinical and research applications. J Am Dent Ass. 2016 Jun;147(6):438–45.
11. Zotti F, Albanese M, Rodella L, Nocini P. Platelet-Rich Plasma in Treatment of Temporomandibular Joint Dysfunctions: Narrative Review. Int J Mol Sci. 2019 Jan;20(2):277–277.
12. Kapos FP, Exposto FG, Oyarzo JF, Durham J. Temporomandibular disorders: a review of current concepts in aetiology, diagnosis and management. Oral Surg. 2020 Nov;13(4):321–34.
13. Al-Moraissi EA, Alradom J, Aladashi O, Goddard G, Christidis N. Needling therapies in the management of myofascial pain of the masticatory

muscles: A network meta-analysis of randomised clinical trials. J Oral Rehabil. 2020 Jul;47(7):910–22.

14. Al-Moraissi EA, Wolford LM, Ellis E, Neff A. The hierarchy of different treatments for arthrogenous temporomandibular disorders: A network meta-analysis of randomized clinical trials. J Craniomaxillofac Surg. 2020 Jan;48(1):9–23.
15. Renapurkar SK, Laskin DM. Injectable Agents Versus Surgery for Recurrent Temporomandibular Joint Dislocation. Oral Maxillofac Surg Clin Nor Am. 2018 Aug;30(3):343–9.
16. PRISMA-P Group, Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015 Dec;4(1):1.
17. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF. Arthritis Care Res. 2011 Nov;63(S11):S240–52
18. Kumari S, Reddy D, Paul S. The normal range of maximal incisal opening in pediatric population and its association with physical variables. Ann Afr Med. 2019;18(3):153–153.
19. Zeng X, Zhang Y, Kwong JSW, Zhang C, Li S, Sun F, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. J Evid Based Med. 2015 Feb;8(1):2–10.
20. Ram H, Shah D. Comparative evaluation of occlusal splint therapy and muscle energy technique in the management of temporomandibular disorders: A randomized controlled clinical trial. J Indian Prosthodont Soc. 2021;21(4):356–65.
21. Sousa B, López-Valverde N, López-Valverde A, Caramelo F, Fraile J, Payo J, et al. Different Treatments in Patients with Temporomandibular Joint Disorders: a Comparative Randomized Study. Medicina (Kaunas) 2020;56(3).
22. Delgado de la Serna P, Plaza-Manzano G, Cleland J, Fernández-de-Las-Peñas C, Martín-Casas P, Díaz-Arribas M. Effects of Cervico-

Mandibular Manual Therapy in Patients with Temporomandibular Pain Disorders and Associated Somatic Tinnitus: a Randomized Clinical Trial. Pain Med. 2020;21(3):613-624.

23. Priyadarshini S, Gnanam A, Sasikala B, Elavenil P, Raja Sethupathy Cheeman S, Mrunalini R, et al. Evaluation of prolotherapy in comparison with occlusal splints in treating internal derangement of the temporomandibular joint - A randomized controlled trial. J Craniomaxillofac Surg. 2021;49(1):24-28.
24. Zarate M, Frusso R, Reeves K, Cheng A, Rabago D. Dextrose Prolotherapy Versus Lidocaine Injection for Temporomandibular Dysfunction: a Pragmatic Randomized Controlled Trial. J Altern Complement med. 2020;26(11):1064-1073.
25. Harba AN, Harfoush M. Evaluation of the participation of hyaluronic acid with platelet-rich plasma in the treatment of temporomandibular joint disorders. Dent med Probl. 2021;58(1):81–8.
26. Patil SR, Aileni KR. Effect of transcutaneous electrical nerve stimulation versus home exercise programme in management of temporomandibular joint disorder. Acta Odontol Scand. 2017;11(12):ZC19–22.
27. Zhang Y, Zhang J, Wang L, Wang K, Svensson P. Effect of transcutaneous electrical nerve stimulation on jaw movement-evoked pain in patients with TMJ disc displacement without reduction and healthy controls. Acta Odontol Scand 2020;78(4):309-320.
28. Özden M, Atalay B, Özden A, Çankaya A, Kolay E, Yıldırım S. Efficacy of dry needling in patients with myofascial temporomandibular disorders related to the masseter muscle. Cranio. 2020;38(5):305-311.
29. Louw W, Reeves K, Lam S, Cheng A, Rabago D. Treatment of Temporomandibular Dysfunction With Hypertonic Dextrose Injection (Prolotherapy): a Randomized Controlled Trial With Long-term Partial Crossover. Mayo Clin Proc. 2019;94(5):820-832.
30. Fertout A, Manière-Ezvan A, Lupi L, Ehrmann E. Management of temporomandibular disorders with transcutaneous electrical nerve stimulation: A systematic review. Cranio. 2019 Nov 9;1–12.

31. Zhang L, Xu L, Wu D, Yu C, Fan S, Cai B. Effectiveness of exercise therapy versus occlusal splint therapy for the treatment of painful temporomandibular disorders: a systematic review and meta-analysis. Ann Palliat Med. 2021 Jun;10(6):6122–32.
32. Saranya B, Ahmed J, Shenoy N, Ongole R, Sujir N, Natarajan S. Comparison of Transcutaneous Electric Nerve Stimulation (TENS) and Microcurrent Nerve Stimulation (MENS) in the Management of Masticatory Muscle Pain: A Comparative Study. Pain Res Manag. 2019 Nov 23;2019:1–5.
33. Zhang SH, He KX, Lin CJ, Liu XD, Wu L, Chen J, et al. Efficacy of occlusal splints in the treatment of temporomandibular disorders: a systematic review of randomized controlled trials. Acta Odontol Scand. 2020 Nov 16;78(8):580–9.
34. Machado E, Machado P, Wandscher VF, Marchionatti AME, Zanatta FB, Kaizer OB. A systematic review of different substance injection and dry needling for treatment of temporomandibular myofascial pain. Int J Oral Maxillofac Surg. 2018 Nov;47(11):1420–32.
35. Nagori SA, Jose A, Gopalakrishnan V, Roy ID, Chattopadhyay PK, Roychoudhury A. The efficacy of dextrose prolotherapy over placebo for temporomandibular joint hypermobility: A systematic review and meta-analysis. J Oral Rehabil. 2018 Dec;45(12):998–1006.
36. Dym H, Bowler D, Zeidan J. Pharmacologic Treatment for Temporomandibular Disorders. Dent Clin North Am. 2016 Apr;60(2):367–79.
37. Bousnaki M, Bakopoulou A, Koidis P. Platelet-rich plasma for the therapeutic management of temporomandibular joint disorders: a systematic review. Int J Oral Maxillofac Surg. 2018 Feb;47(2):188–98.
38. Machado E, Bonotto D, Cunali PA. Intra-articular injections with corticosteroids and sodium hyaluronate for treating temporomandibular joint disorders: a systematic review. Dental Press J Orthod. 2013 Oct;18(5):128–33.
39. Sit RWS, Reeves KD, Zhong CC, Wong CHL, Wang B, Chung VC ho, et al. Efficacy of hypertonic dextrose injection (prolotherapy) in temporomandibular joint dysfunction: a systematic review and meta-analysis. Sci Rep. 2021 Dec;11(1):1463

40. Lee E, Crowder HR, Tummala N, Goodman JF, Abbott J, Zapanta PE. Temporomandibular disorder treatment algorithm for otolaryngologists. Am J Otolaryngol. 2021 Nov;42(6):103155.

ANNEXES

ANNEX 1: Diagram 1: Taxonomy of temporomandibular disorders' diagram

ANNEX 2: Exact keywords by Database

ANNEX 3: Scheme 1: Search strategy Flow chart

ANNEX 4: Table 2: CASP Selective criteria

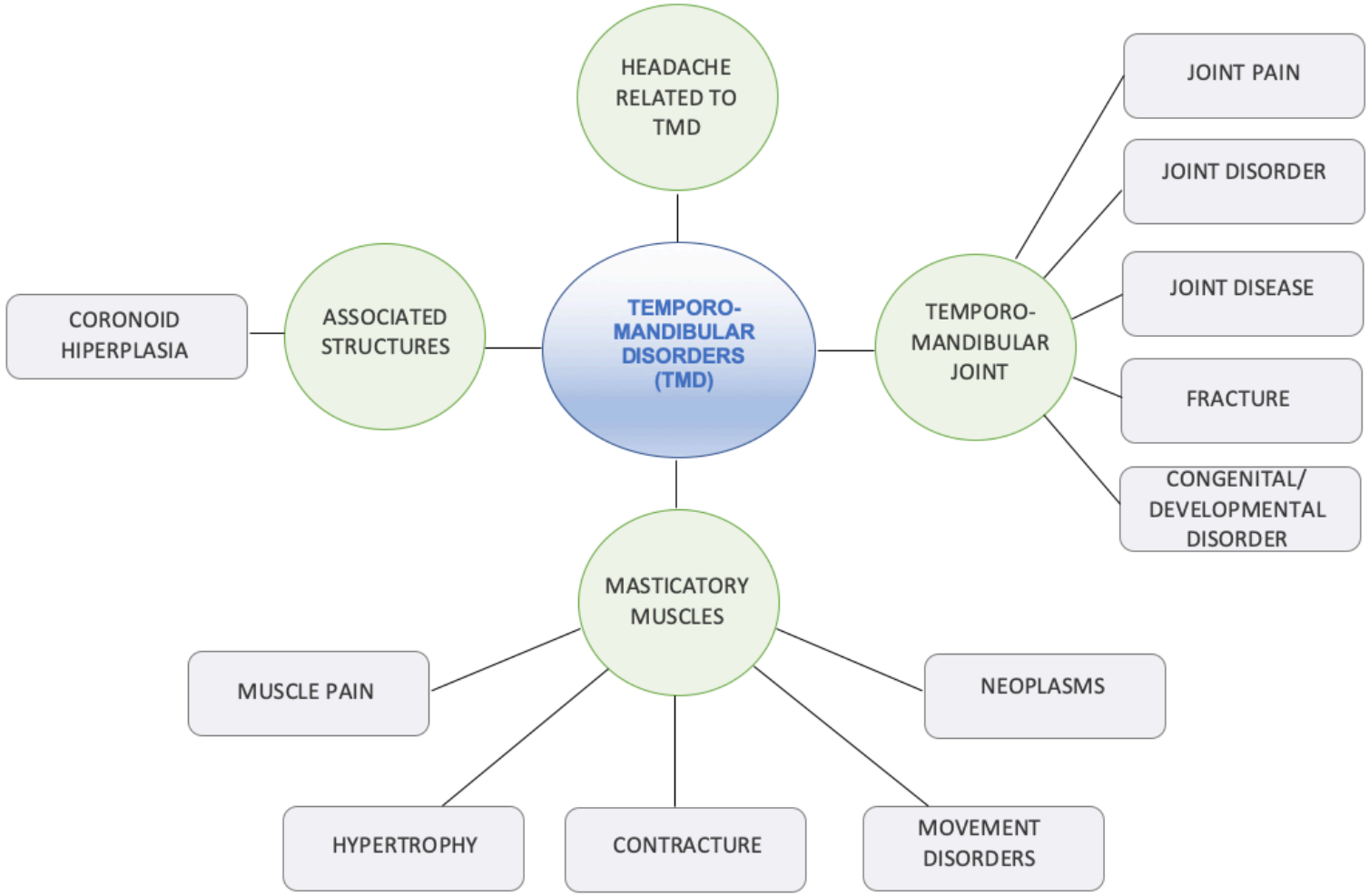
ANNEX 5: Table 3: Trials characteristics

ANNEX 6: Table 4: Subgroups, interventions, follow-up frequency and outcomes results

ANNEX 7: PRISMA Checklist

ANNEX 8: Article version

ANNEX 1: Diagram 1: Taxonomy of temporomandibular disorders' diagram



ANNEX 2: Exact keywords by Database

SCOPUS:

TITLE-ABS
KEY (((randomized AND controlled AND trials) OR rct) AND ((((temporomandibular AND joint OR tmj) OR temporomandibular AND disorders OR tmd)) AND (((conservative AND therapy) OR (dry AND needle OR acupuncture) OR pharmacotherapy OR ((manual AND therapy) OR physiotherapy) OR ((oral AND appliance) OR splint) OR tens) OR ((injection) OR (wet AND needling) OR (botulinum AND toxin) OR dextrose OR (hyaluronic AND acid) OR (platelet AND rich AND plasma) OR corticosteroid)))) AND (LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017)) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (EXACTKEYWORD , "Human") OR LIMIT-TO (EXACTKEYWORD , "Humans")) AND (LIMIT-TO (EXACTKEYWORD , "Randomized Controlled Trial")) AND (LIMIT-TO (EXACTKEYWORD , "Pain Measurement") OR LIMIT-TO (EXACTKEYWORD , "Visual Analog Scale") OR LIMIT-TO (EXACTKEYWORD , "Pain Intensity") OR LIMIT-TO (EXACTKEYWORD , "Quality Of Life") OR LIMIT-TO (EXACTKEYWORD , "Range Of Motion, Articular") OR LIMIT-TO (EXACTKEYWORD , "Range Of Motion") OR LIMIT-TO (EXACTKEYWORD , "Pain Threshold") OR LIMIT-TO (EXACTKEYWORD , "Mouth Opening"))

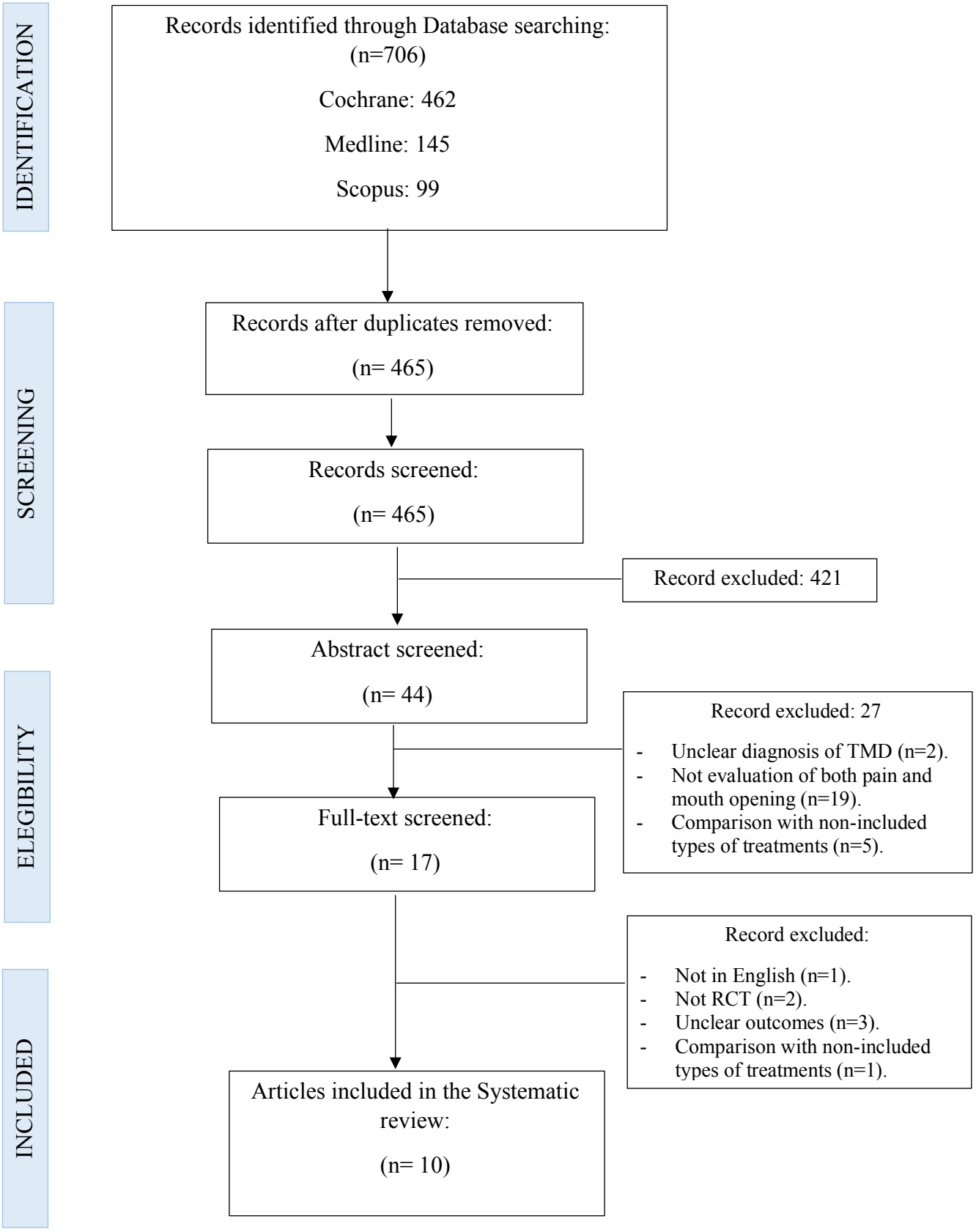
Cochrane

(((Temporomandibular joint OR TMJ) OR ((temporomandibular disorders) OR TMD)) AND (((conservative therapy) OR (Dry needle OR acupuncture) OR Pharmacotherapy OR ((Manual therapy) OR physiotherapy) OR ((oral appliance) OR Splint) OR TENS) OR ((injection) OR (wet needling) OR (Botulinum Toxin) OR Dextrose OR (hyaluronic Acid) OR (Platelet Rich Plasma) OR Corticosteroid) in Title Abstract Keyword - with Cochrane Library publication date from Jan to present (Word variations have been searched)

Medline

(((Temporomandibular joint OR TMJ) OR ((temporomandibular disorders) OR TMD)) AND (((conservative therapy) OR (Dry needle OR acupuncture) OR Pharmacotherapy OR ((Manual therapy) OR physiotherapy) OR ((oral appliance) OR Splint) OR TENS) OR ((injection) OR (wet needling) OR (Botulinum Toxin) OR Dextrose OR (hyaluronic Acid) OR (Platelet Rich Plasma) OR Corticosteroid)) Filters: Randomized Controlled Trial, in the last 5 years, Humans, English, MEDLINE

ANNEX 3: Scheme 1: Search strategy flow chart



ANNEX 4: Table 2: CASP Selective criteria

	Ram[20] et al.	Sousa[21] et al.	Delgado de la Serna[22] et al.	Priyadarshini[23] et al.	Zarate[24] et al.	Harba[25] et al.	Patil[26] et al.	Zhang[27] et al.	Özden[28] et al.	Louw[29] et al.
Clearly focused question	+	+	+	+	+	+	+	+	+	+
Randomized	+	+	+	+	+	+	+	+	+	+
Same n° of patients at the beginning & the end	-	?	-	+	-	?	?	+	+	-
Participants, investigators and people analyzing are blinded	-	?	+	+	+	?	-	-	?	+
Study groups similar at the start	?	+	+	-	+	-	+	+	+	-
Same level of care for each group	+	+	+	+	+	+	+	+	-	+
Effects comprehensively reported	+	+	+	+	+	+	+	+	+	+
Reports of the estimate of the intervention or treatment effect	+	+	+	-	+	-	-	-	+	-
The benefits of RCT outweigh the harms and costs	+	+	+	+	+	+	+	+	+	+
Results applicable to our population/ dental clinic	+	+	+	+	+	+	+	+	+	+
Provide greater value to the people in the care than any of existing interventions	+	+	+	+	+	+	+	+	+	+
TOTAL SCORE	8	9	10	9	10	7	9	9	9	8

ANNEX 5: Table 3: Trials' Characteristics

AUTHOR AND YEAR	STUDY DESIGN	N° OF PATIENTS	AGE OF PATIENTS	MALE-FEMALE RATIO	DIAGNOSTIC CRITERIA	OUTCOME
Ram et al. 2021[20]	Prospective Multicenter Double-blinded RCT	n=120	39.44±10.34.	45.63/ 54.37%.	DC-TMD Axis 1: Local myalgia, myofascial pain, myofascial pain with referral, arthralgia, headache, disc displacement with reduction/ with reduction with intermittent locking/ without reduction with limited opening/ without reduction without limited opening/ degenerative joint disease.	VAS MMO
Sousa et al. 2020[21]	RCT	n=80	43.1 (SD 17.7)	20/80%	DC-TMDs: TMJ arthralgia.	VAS MMO
Delgado et al. 2020[22]	Double-blinded RCT multicenter	n=61	Group1: 44.0 ± 10.5 Group 2: 42.5±12.0	40.98/59.02%	RDC-TMD associated with tinnitus.	NPRS MRM
Priyadarshini et al. 2021[23]	Double-blinded RCT	n=34	Group 1: 31.79 Group 2: 28.35	35.3/64.7%	TMD confirmed by MRI: Wilkes stage II and III TMJ internal derangement.	VAS MMO
Zarate et al. 2020[24]	Double-blinded RCT	n=29	47±18	14/86%	RDC-TMD I (myofascial), II (disc displacement) and III (other joint dysfunctions).	NRS MIO
Harba et al. 2021[25]	Single-blind RCT	n=24	30.58±23.92	NC	Wilkes classification: III (intermediate), IV (late intermediate) & V (late stage).	VAS MMO
Patil et al. 2017[26]	RCT	n=36	Group 1: 34±7.4 Group 2: 32.91±12.57	36.20/ 63.79%	RDC-TMD	VAS MMO
Zhang et al. 2020[27]	Single-blinded RCT	n=40	25-38.	NC	DC-TMD: arthralgia + MRI: TMJ disc displacement without reduction	NRS TOD
Özden et al. 2020[28]	RCT	n=60	18-65.	48/ 52%	RDC-TMD: Group I MTMD	VAS MMO
Louw et al. 2019[29]	Double-blinded RCT	n=44	46±14	16.7/83.3%	RDC-TMD I (myofascial), II (disc displacement) and III (other joint dysfunctions).	NRS MMO

**RCT: Randomized controlled trial/ NC: Non-communicated/ RDC-TMD: Research Diagnostic Criteria for temporomandibular disorders/ DC-TMD: Diagnostic criteria for temporomandibular disorders/MTMD: Myofascial temporomandibular disorder/ VAS: Visual analogue scale/ NRS: Numeric Rating Scale/ MMO: Maximum mouth opening/ MRM: Mandibular range of motion/ MIO: Maximum interincisal opening/ TOD: Total oral distance.*

ANNEX 6: Table 4: Subgroups, interventions, follow-up frequency and outcomes results

AUTHOR AND YEAR	SUBGROUPS	INTERVENTIONS	FOLLOW-UP FREQUENCY	OUTCOMES RESULTS
Ram et al. 2021[20]	Group 1: Muscle energy technique (n=40). Group 2: Occlusal splint therapy (n=40). Group 3: Combined treatment (n=40). Group 4: Control group (n=40).	○ Muscle energy technique: Post-isometric relaxation & reciprocal inhibition. (3 times/weeks for 4 weeks). ○ Occlusal splint therapy. ○ Muscle energy technique + Occlusal splint therapy. ○ Education for self-management & counseling.	1 week, 2 week, 1 months and after 3 months	Highly significant reduction of pain for groups 1, 2 and 3 as compared to the control group and no significant difference between groups 1, 2, 3. Highly significant improvement of mouth opening for group 1 and 3 as compared to group 2 and 4 and no significant difference between group 1 and 3.
Sousa et al. 2020[21]	Group 1 (Control group): Bite splint therapy (n=20). Group 2: Bite splint and betamethasone. (n=20). Group 3: Bite splint and sodium hyaluronate (n=20). Group 4: Bite splint and Platelet-rich plasma (n=20).	○ Bite splint with contact in all teeth and canine guidance. ○ Bite splint and pre-auricular injection of 1mL of betamethasone (Diprofofos Depot 7mg/mL). ○ Bite splint and pre-auricular injection of 1L of sodium hyaluronate (Hyalart 10mg/Ml). ○ Bite splint and pre-auricular injection of 2mL of PRP from ulnar vein.	1 week, 1 month, 6 months	All 4 types of treatments showed pain reduction and better mouth opening. Significant pain reduction in all groups treated with injection: lower reduction in group 1 and higher in group 4. Significant increase of pain-free mouth opening in all groups: smaller average rate per week in group 1 and larger in group 4.
Delgado et al. 2020[22]	Group 1 (Control): Exercise + education (n=30). Group 2: Exercise + Education + Manual therapy (n=31).	○ Exercise therapy program (twice/day): Mobility, postural education and motor control exercises of the TMJ, the tongue and the neck; instructions for resting jaw position, neck/head postures. ○ Cervico-mandibular manual therapy group: Manual therapy techniques focusing on the TMJ and the masticatory and cervical musculature.	3 month, 6 months	Greater reduction of pain and mandibular range of motion among group 2.

Priyadarshini et al. 2021[23]	Group 1 (Control): Anterior bite planes (n=17) Group 2: Anterior bite plane + Prolotherapy (n=17)	○ Anterior bite planes for 12h/ day up to 3 months. ○ Injection of Prolotherapy solution in posterior joint space, anterior disc attachment to the lateral pterygoid muscle, and masseter attachment at day 1, 2 weeks, 6 weeks and 12 weeks: dextrose 50% (0.75ml), lignocaine 2% with adrenaline (1.5ml) and bacteriostatic water (0.75ml)	1 month, 3 months, 6 months, 1 year	Statistically reduction of pain and improvement of mouth opening in group 2.
Zarate et al. 2020[24]	Group 1 (Control): Lidocaine injections (n=15) Group 2: Lidocaine and Dextrose injections (n=14)	○ Intra-articular injections of Dextrose 20%/lidocaine 0.2% at day one, one month, 2 months and by demand after 3 months. ○ Intra-articular injection of sterile water/lidocaine 0.2% at day one, one month, 2 months and by demand after 3 months.	0,1, 2, 3 months (and by request in the following year).	No significant difference between groups regarding pain reduction. However, group 2 showed a more frequent ≥50% pain improvement group 1. Substantial improvement of MIO for both groups.
Harba et al. 2021[25]	Group 1 (control): HA injection (n=12). Group 2: HA + PRP injections	○ 4 intra-articular injection sessions of 1mL of HA /session with 14 days between sessions. ○ Intra-articular injection of 0.5mL of HA + 0.5ml of PRP / session for 4 sessions with a 14-day interval between sessions.	0, 2 weeks, 1 months, 3 months and 6 months.	In both groups: a statistically significant pain reduction after 2 weeks and after 1-month follow-up. In group 1: a significant increase of pain between 3 to 6 months. In both groups: a significant increase of between day 0 and after 2 weeks. However, for group 1, there was a significant decrease of MMO between 1 and 3 months.
Patil et al. 2017[26]	Group 1(Control group): Home exercise (n=18) Group 2: TENS (n=18).	○ Home exercise: education, active and passive jaw opening and closing exercises, isometric jaw exercises, jaw stretching exercises and resistive jaw exercises: twice a day for 4 weeks. ○ TENS therapy during 30mn once a week for a period of 4 consecutive weeks.	0, 1, 2, 3 and 4 weeks.	For both groups: significant decrease of pain between each session, except between 0 to 1 week for group 1. For both groups: significant improvement of MMO between each session but no significant difference between groups.

Zhang et al. 2020[27]	Group 1: Control TENS (n=10) Group 2: Control sTENS (n=10) Group 3: TENS (n=10) Group 4: sTENS (n=10)	○ TENS: Electrical stimulation over both TMJ region 45 min with a green light flashing. ○ sham TENS (sTENS): Same without electrical output.	Before and after intervention.	A significant decrease of NRS pain in group 3 after treatment. No significant difference of TOD before and after TENS intervention but a significant decrease of TOD in the 5th session in group 4.
Özden et al. 2020[28]	Group 1 (Control): Healthy patients without treatment (n=20) Group 2: Superficial dry needling (n=20) Group 3: Deep dry needling (n=20)	○ Superficial dry needling: Intramuscular needling depth up to 5mm in the masseter trigger point during 20mn/weeks over 3 weeks. ○ Deep dry needling: Intramuscular needling depth at least 10mm in the masseter trigger point during 20mn/weeks over 3 weeks.	0, 3 and 6 weeks.	No significant difference between 3 to 6 weeks regarding VAS for pain and MMO for both groups. The trigger point palpation VAS scores in 3rd and 6th weeks were better than the baseline values in both groups.
Louw et al. 2019[29]	Group 1 (Control): 0.2% Lidocaine (n=20). Group 2: Dextrose injection (n=22).	○ Intra-articular injection in the superior joint space of 0.2% lidocaine every month for 2 months. ○ Intra-articular injection in the superior joint space of 20% Dextrose/ 0.2% lidocaine every month for 2 months.	0, 1, 2, 3 months	Higher change in NRS pain in group 2 than group 1 Group 2 showed a higher improvement in MIO than group 1 during the 3 months masked treatment period.

ANNEX 6: PRISMA checklilist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	7
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	21
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	21
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	23
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	23
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	23-25
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	26
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	27
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	27
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	27
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	27-28
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data	

Section and Topic	Item #	Checklist item	Location where item is reported
		conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	29
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	29
Study characteristics	17	Cite each included study and present its characteristics.	29-30
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	29
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			

Section and Topic	Item #	Checklist item	Location where item is reported
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	34-41
	23b	Discuss any limitations of the evidence included in the review.	42
	23c	Discuss any limitations of the review processes used.	42
	23d	Discuss implications of the results for practice, policy, and future research.	42
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

ANNEX 7: Article presentation

TITLE: "Comparison of the effectiveness between peri/ intra-articular injections and conventional treatments in patients with temporomandibular disorders' symptoms: A systematic review"

RUNING TITLE: Peri/ intra-articular injections or conventional treatments in TMD management

AUTHORS: Laetitia Massé, Ana Candel Tomás, Maria Gracia Sarrión Pérez, Santiago Arias-Herrera.

AFFILIATIONS: Universidad Europea de Valencia. Faculty of Health Sciences. Department of dentistry.

Laetitia MASSÉ; 24 rue de la ferme; 94210 La Varenne Saint-Hilaire; FRANCE

Email: 21703069@live.uem.es

KEYWORDS: Temporomandibular joint; Temporomandibular disorders; Conventional therapy; Minimally invasive treatment; Peri/ Intra-articular injection.

ABSTRACT:

Introduction: Temporomandibular disorders (TMD) is a generic term to described a group of related musculoskeletal signs and symptoms involving the temporomandibular joint, the masticatory muscles and other associated structures. Intra/peri-articular injections of various products is a part of the minimally invasive treatments for TMD management with affordable agents that are easy to obtain and could be applied in outpatient office setting. **Objective:** The aim of this study was to compare the effectiveness between peri/ intra-articular injections and conventional treatments in patients with TMD on pain management and TMJ's mobility. **Material and methods**: A comprehensive research in MEDLINE, SCOPUS and Cochrane Central Registry of Controlled Trials was conducted from January 2022 to April 2022. **Results**: Ten studies were included ranging from moderate to high methodological quality. Five RCT compared different conventional therapies between them, three analyzed the difference between intra/peri-articular injection's products and two RCT

compared conservative therapies to intra/peri-articular injection's treatment. **Conclusion:** Peri/intra-articular injections showed a higher effect on mouth aperture based on maximal mouth opening. Both conventional and peri/intra-articular injections displayed an equivalent pain diminution using visual analogue or numerical rating scale. In order, from the most effective therapies to the least, the following classification was established: combination of occlusal splint with intra-articular injection of PRP/ Bethamethasone/ Sodium Hyaluronate, muscular exercise, manual therapy, intra-articular injection of HA and PRP, splint therapy, intra-articular injection of Lidocaine and Dextrose, TENS and Dry Needling.

INTRODUCTION

Temporomandibular joint (TMJ) is a ginglymoarthroidial synovial joint connecting the skull to the mandible base which is implied in both language and mastication. (1)

Temporomandibular disorders (TMD) is a generic term to described a group of related musculoskeletal conditions involving the temporomandibular joint, the masticatory muscles and other associated structures. It affects 10-15% of adults and 4-7% of adolescents in both developed and developing countries. (2, 3) The most common symptoms are pain, limited range of motion and TMJ sounds. (4)

TMD could be classified in four groups: temporomandibular joint disorders, masticatory muscle disorders, headache related to temporomandibular disorders and associated structures disorders. (5)

The most worldwide accepted diagnostic criteria was RDC/TMD which was revised and replaced by the DC/TMD in 2014. These diagnostic criteria are based on two axes: Axis I (physical) and Axis II (psychosocial). (6, 7)

The first line of management is made by conservative treatments including patient's educations and self-management, medications, intraoral appliances, physiotherapy and low-level laser therapy. The second line is formed by less-invasive treatments such as intra-articular injections (IAI), arthrocentesis with or without occlusal splints, arthroscopy alone or in combination with IAI. The last one corresponds to surgical treatments including minimally invasive

arthroscopic procedures or invasive open joint surgeries. (8) Depending on each patient, a multimodal strategy may be included in the treatment plan.(9)

Injections of various products have been used to treat different types of TMD. Wet needling consists of intramuscular injections. It's made by hollow-bore needles to transfer substances such as Botulinum toxin, corticosteroids, local anesthetics solutions, sclerosants or saline solutions. (10)

The aim of this study was to compare the effectiveness between peri/ intra-articular injections and conventional treatments in patients with TMD on pain management and TMJ's mobility.

MATERIAL AND METHODS

Protocol

This systematic review was realized based on the Preferred reporting Items for the PRISMA Extension Statement for reporting of Systematic Reviews Incorporating Network Meta-Analyses of Health Care Interventions (PRISMA-P checklist). (11)

Search strategy

All pertinent Randomized Controlled Trials (RCTs) in English were screened by comprehensive research in MEDLINE, SCOPUS and Cochrane Central Registry of Controlled Trials from January 2022 to April 2022.

The following key words were used: ((Temporomandibular joint OR TMJ) OR (temporomandibular disorders OR TMD) AND ((conservative therapy) OR (Dry needle OR acupuncture) OR Pharmacotherapy OR ((Manual therapy) OR physiotherapy) OR ((oral appliance) OR Splint) OR TENS) OR ((injection) OR (wet needling) OR (Botulinum Toxin) OR Dextrose OR (hyaluronic Acid) OR (Platelet Rich Plasma) OR Corticosteroid).

Selection criteria

The inclusion criteria were based on the PICOTS process: (P) Patients: Patients with arthrogenous or muscular TMD based on the RDC/TMD or

DC/TMD protocol or clear diagnosis with signs and symptoms of TMD; (I): Peri/Intra-articular injection's treatment 1) HA intra-articular injections; 2) Corticosteroid intra-articular injections; 3) BoNT-A injection; 4) PRP injections; 5) Dextrose injection; (C) Comparator: Conservative therapy 1) Muscular exercise; 2) Manual therapy 3) Intra-oral appliance (orthodontic appliance and stabilization splint); 4) Dry Needle techniques; 5) TENS; (O) Outcomes: The first outcome is a decreased in pain intensity scores using a visual analogue scale (VAS) and a numerical pain rating scale. The second outcome is an improvement in mouth opening using interincisal measurement; (T): short time (≤ 5 months) and intermediate time (≥ 6 months to 4 years); (S) Study design: RCTs of the last five years containing the outcomes of interest and the comparator.

Exclusion criteria

The following exclusion criteria were applied: 1) RCTs comparing one of the outcomes with surgical treatments. 2) RCTs in which the injections products are used in adjunction of arthroscopy or arthrocentesis. 3) Headaches not associated with arthrogenous or muscular TMD. 4) Bruxism not clearly identified as a TMD symptom. 5) Full-text not in English. 6) Unclear outcomes.

Data extraction

A data extraction was made by an operator. The extraction form was later revised by another reviewer. The extracted data are RCTs characteristics including author, study design, subgroups, diagnostic criteria used, age of patients, male-female ratio, interventions, duration of treatment/frequency and outcomes measures.

Quality assessment

Critical Appraisal Skills Program (CASP) Randomized Controlled Trial Standard Checklist (12) was used to assess the methodological quality of each article.

RESULTS

Trial selection

The electronic search on the 3 databases resulted in 706 published references. After removing all the duplicates, only 465 references remained. After screening the tittles, 44 abstracts were analyzed. Among them, 27 were excluded for the following reasons: unclear diagnosis of TMD (n=2), not evaluation of both pain and mouth opening (n=19), comparison with non-included types of treatments (n=5). 17 full-text articles were screened and 7 were excluded for the following reasons: not in English (n=1), not RCT (n=2), unclear outcomes (n=2), comparison with non-included types of treatments (n=1). Ten references were included (*Scheme 1*) in this systematic review: all the articles were RCT. (13-22)

Trial characteristics

The trial characteristics are exposed in *Table 1*.

Effects on pain and mouth opening

Outcomes analysis are displayed in *Table 2*. The reported immediate effect of TENS' application in one trial was a pain reduction and no significant effect on total oral opening. (20) Another study (19) demonstrated a significant decrease of pain and a significant improvement of MMO between each session for both TENS and muscular exercise group without any significant difference between both groups. In comparison with a control group receiving educational counselling, the other groups submitted to muscle energy technique, occlusal splint therapy or combined treatment, showed a significant reduction of pain after 3 months and no significant difference between them. However, it was the muscle energy technique group and combined group that showed a highly significant improvement of maximum mouth opening after 3 months. (27) In another trial (29), combination of exercise, education and manual therapy group showed a greater reduction of pain and a higher increase of mandibular range of motion than those receiving exercise/education alone. The application of superficial or deep dry needling technique showed a reduction of pain at trigger palpation points after 3 and 6 weeks. (21)

Compared to a control group with bite splint only, there was a significant improvement of both pain and mouth opening in the groups providing a combination of bite splint and peri-auricular injection of betamethasone,

sodium hyaluronate or PRP, with a higher reduction in the bite splint and PRP group.(14) In another study, the combination of anterior bite splint and prolotherapy showed a significant reduction of pain and improvement of mouth opening after 1 year in comparison to anterior bite plane alone.(16)

At 3 months, one trial (17) showed no significant difference of pain between intra-articular injection of lidocaine alone, or in combination with dextrose. However, the last group showed a more frequent increase at least of 50% of pain improvement than the control group. Both of them had a substantial improvement of MIO. Another study (22) demonstrated a higher reduction of pain and improvement of MIO after 3 months with injection of a combination of dextrose and lidocaine rather than lidocaine alone. Intra-articular injection of HA alone or in combination with PRP showed a significant pain reduction at 1-month follow-up. However, lidocaine alone provided a significant increase of pain between 3 to 6 months and a significant decrease of MMO between 1 and 3 months. (17)

Quality assessment

Quality scores (*Table 3*) of the including studies ranged from moderate (13, 18, 22) to high (14, 15, 16, 17, 19, 20, 21) methodological quality.

DISCUSSION

Conservative therapies

TENS application's protocol was different between both selected studies (19, 20) regarding their protocol, duration of session and especially duration of treatment. Fertout et al (23) showed that TENS was effective on both arthrogenous and/or muscular TMD and constitutes an effective non-drug based conservative therapy's option in the management of TMD. One of the present RCT (19) showed a significant higher pain improvement for TENS therapy in comparison to home exercise program. Therapeutic exercises stimulate the parasympathetic activity. (24) Whereas TENS application is based on several interrelated theories: the gate-control theory, the endogenous release of morphine-like substance

after electrical stimulation and muscles' automatic and involuntary contraction. (25)

Two studies (13, 15) revealed the efficacy of manual techniques on pain and jaw aperture in TMD patients. One of them showed the interest to combine it with exercise and education. Both manual therapy and therapeutic exercise have a neurophysiological effect within the central nervous system. A multimodal therapy allows a multidimensional effect on TMD patients. An osteopathic muscular energy technique alone or in combination with an occlusal splint showed a better efficacy in comparison to a combination of education and counseling. Muscular energy technique acts on Golgi tendon receptor by stretching muscle fibers that inhibits muscle tension and leads to relaxation. (15) Occlusal splint therapy presented a similar effect on pain than muscular energy technique or the combinations of both and a lower effect on maximal mouth opening. (13) Splint allows a relaxation of masticatory muscles and a condyle centric relation reducing joint's overloading and favoring a normalization of blood supply. (15) Zhang (26) et al. found different results and recommended in their systematic review occlusal splint as an election treatment for TMD patients with signs and symptoms of mandibular restrictions whereas in patients with TMD-related pain a combination of education, occlusal splint and manual therapy was suggested.

One RCT demonstrated that dry needling allowed an improvement in TMD-related pain but had no significant effect on maximum mouth opening. The authors recommended a multimodal approach when applying it. (21) Dry needling is based on intramuscular stimulation and mechanical disruptions of muscle fibers and nerve endings, as well as electrical activity's reduction. (27)

Conservative and injections therapies

The combination of prolotherapy and occlusal splint showed a long-term relief of TMD symptoms and has been recommended as a therapeutic option in the management of TMJ's internal derangement. (14, 16) Even, if prolotherapy has proved is efficacity in other joints such as knee, it's a relatively new method in the management of TMD. The effect of dextrose prolotherapy is based on

inflammatory and non-inflammatory process regarding the concentration of dextrose. A dextrose solution superior to 10% allows the deposit of new cells and tissue matrix in the joint with tissue maturation between 6 to 8 weeks. (28)

The combined application of bite splint with hyaluronate acid showed similar effects than its combination with betamethasone. Both of these substances present a potent anti-inflammatory effect on synovial tissue allowing a reduction of effusion and pain, and an increased range of motion. (14, 29)

It was also demonstrated that the application of PRP and occlusal splint led to a better effect on both pain and mouth aperture in TMD patients after 6 months. (14) PRP mechanisms are still under investigation but it seems to provide an anti-inflammatory, analgesic and chondrogenic effect in the joint. (30)

Injections therapies

Even if both injections of HA alone or in combination with PRP showed their efficacity on pain and jaw opening, only the combination of both products offered long-term better results. (22) Viscosuplementation with HA provides tissue lubrication, nutrition and analgesic effect. It also promotes the release of adhesion area between the disc and mandibular fossa favoring joint mobility. (31) In combination with PRP's properties, it constitutes a minimally invasive option in TMD management that doesn't require surgical incision.

A combination of dextrose and lidocaine injections had a higher efficacy than lidocaine alone. (17, 22) Sit et al. (32) recommended the application of dextrose injection in patients with internal derangement of TMJ that are refractory to conventional therapy.

Conservative Vs Injections therapy

The first intervention for TMD management should be based on education and home exercise as these are non-invasive methods that can quickly be set up. (13, 15) Then, the management should be based on TMD types as well as signs and symptoms.

Myogenous TMD patients with pain could be treated with dry needling. However, if patients show mouth opening limitations too, other types of

conservative therapies should be added. (21) According to Machado et al. (27), several substances injections could also be considered in case of myogenous TMD-related pain such as local anesthetics and corticosteroids.

In case of arthrogenous TMD, various therapies could be implemented regarding patients' preferences, intensity and duration of their signs and symptoms. For patients with arthrogenous TMD-related pain and mouth-opening limitation, bite splint, cervico-mandibular manual therapy, TENS and intra-articular injections could be proposed. (14, 15, 16, 18, 20) If there is a marked limitation of jaw aperture, TENS should not be suggested or only in addition to other therapy as it provides a delayed effect on jaw opening. (20) For persistent or intense pain, it should be recommended to use a multimodal therapy with a combination of a bite splint and injections products such as corticosteroid, HA, dextrose or PRP. (14, 16,18) Out of the injection product, PRP seems to be the one providing a better and longer effect. (14, 18)

Mixed TMD management should involve various conservative and intra-articular injection therapy options. Occlusal splint, Muscular energy therapy, TENS, prolotherapy and lidocaine's injection could be suggested. In case of TMD-related pain, TENS, manual therapy, occlusal splint and prolotherapy should be recommended. (13, 17, 19, 22) Prolotherapy seems to constitute a good option for a long-term management. (17) In case of mouth opening's dysfunction, TENS, manual therapy, injection of lidocaine or prolotherapy showed also good results. (13, 17, 19, 22)

Lee et al. (33) created an evidence-based algorithm for the management of TMD to simplify the decision-making process based also on TMD types.

Limitations

This systematic review only included studies in English which may lead to publication bias. Furthermore, it excluded arthrocentesis and arthroscopy studied in combination with injection, as it was chosen to focus only of the intra/peri-articular injections among the minimally invasive therapies.

The critical analyze of the evidence showed that the selected studies had different diagnosis criteria for TMD. Three studies (13, 14, 20) used

DC/TMD, five (15, 17, 19, 21, 22) RDC/TMD, and two (16, 18) Wilkes classification. Half of the studies (14, 15, 16, 18, 20) were focused on arthrogenous TMD, one (35) on myogenous TMD and four (13, 17, 19, 22) on both arthrogenous and myogenous TMD. Furthermore, various others limitations of varying degree were fund in the included studies: small sample size (16, 17, 19, 20, 21, 22), short follow-up period (16, 19, 21) and only one study (21) among the ten included had a control group without any interventions.

Further studies are recommended and should include: 1) high methodological quality RCT 2) with larger sample size; 3) long-term follow-up; 4) arthrogenous or myogenous TMD based on the same criteria; 5) direct comparison of conservative and peri/intra-articular injections therapies; 6) a control group without any intervention.

CONCLUSION

Peri/intra-articular injections allowed a higher effect on mouth aperture based on maximal mouth opening or equivalent assessment tool.

Both conventional and peri/intra-articular injections showed a significant pain reduction among TMD patients, displaying an equivalent diminution regarding pain evaluation by visual analogue scale or numerical rating scale.

Based on pain scale and maximal mouth opening or equivalent assessment tool, the most effective therapy for the management of TMD patients with pain and limited mouth opening is the combination of splint with intra-articular injection of PRP, bethamethasone or sodium hyaluronate. The second and third most effective options are formed by conservative therapies: muscular exercise and manual therapy. The fourth most effective is made by the intra-articular injection of HA and PRP, followed by splint therapy and intra-articular injection of lidocaine and dextrose. The least effective ones are constituted by TENS and Dry needling.

ACKNOWLEDGEMENT

Authors would like to thank Dental department of European University of Valencia and researchers for their help with this systematic review.

CONFLICT OF INTEREST

No conflicts of interest in this study.

ROLE OF THE FUNDING SOURCE

No external funding apart from the support of the author's institution, was available for this study.

REFERENCES:

1. Salamon NM, Casselman JW. Temporomandibular Joint Disorders: A Pictorial Review. Semin in Musculoskelet Radiol. 2020 Oct;24(05):591–607.
2. Chang CL, Wang DH, Yang MC, Hsu WE, Hsu ML. Functional disorders of the temporomandibular joints: Internal derangement of the temporomandibular joint. Kaohsiung J Med Sci. 2018 Apr;34(4):223–30.
3. Ohrbach R, Dworkin SF. AAPT Diagnostic Criteria for Chronic Painful Temporomandibular Disorders. J Pain. 2019 Nov;20(11):1276–92.
4. Fernandes G, Gonçalves DAG, Conti P. Musculoskeletal Disorders. Dent Clin Nor Am. 2018 Oct;62(4):553–64.
5. Schiffman E, Ohrbach R. Executive summary of the Diagnostic Criteria for Temporomandibular Disorders for clinical and research applications. J Am Dent Ass. 2016 Jun;147(6):438–45.
6. Ohrbach R, Dworkin SF. The Evolution of TMD Diagnosis. J Dent Res. 2016 Sep;95(10):1093–101.
7. List T, Jensen RH. Temporomandibular disorders: Old ideas and new concepts. Cephalalgia. 2017 Jun;37(7):692–704.
8. Al-Moraissi EA, Alradom J, Aladashi O, Goddard G, Christidis N. Needling therapies in the management of myofascial pain of the masticatory muscles: A network meta-analysis of randomised clinical trials. J Oral Rehabil. 2020 Jul;47(7):910–22.
9. Kapos FP, Exposto FG, Oyarzo JF, Durham J. Temporomandibular disorders: a review of current concepts in aetiology, diagnosis and management. Oral Surg. 2020 Nov;13(4):321–34.
10. Al-Moraissi EA, Wolford LM, Ellis E, Neff A. The hierarchy of different treatments for arthrogenous temporomandibular disorders: A network meta-analysis of randomized clinical trials. J Craniomaxillofac Surg. 2020 Jan;48(1):9–23.
11. PRISMA-P Group, Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015 Dec;4(1):1.
12. Zeng X, Zhang Y, Kwong JSW, Zhang C, Li S, Sun F, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. J Evid Based Med. 2015 Feb;8(1):2–10.
13. Ram H, Shah D. Comparative evaluation of occlusal splint therapy and muscle energy technique in the management of temporomandibular disorders: A randomized controlled clinical trial. J Indian Prosthodont Soc. 2021;21(4):356–65.
14. Sousa B, López-Valverde N, López-Valverde A, Caramelo F, Fraile J, Payo J, et al. Different Treatments in Patients with Temporomandibular Joint Disorders: a Comparative Randomized Study. Medicina (Kaunas) 2020;56(3).
15. Delgado de la Serna P, Plaza-Manzano G, Cleland J, Fernández-de-Las-Peñas C, Martín-Casas P, Díaz-Arribas M. Effects of Cervico-Mandibular Manual Therapy in Patients with Temporomandibular Pain Disorders and Associated Somatic Tinnitus: a Randomized Clinical Trial. Pain Med. 2020;21(3):613-624.

16. Priyadarshini S, Gnanam A, Sasikala B, Elavenil P, Raja Sethupathy Cheeman S, Mrunalini R, et al. Evaluation of prolotherapy in comparison with occlusal splints in treating internal derangement of the temporomandibular joint - A randomized controlled trial. J Craniomaxillofac Surg. 2021;49(1):24-28.
17. Zarate M, Frusso R, Reeves K, Cheng A, Rabago D. Dextrose Prolotherapy Versus Lidocaine Injection for Temporomandibular Dysfunction: a Pragmatic Randomized Controlled Trial. J Altern Complement med. 2020;26(11):1064-1073.
18. Harba AN, Harfoush M. Evaluation of the participation of hyaluronic acid with platelet-rich plasma in the treatment of temporomandibular joint disorders. Dent med Probl. 2021;58(1):81–8.
19. Patil SR, Aileni KR. Effect of transcutaneous electrical nerve stimulation versus home exercise programme in management of temporomandibular joint disorder. Acta Odontol Scand. 2017;11(12):ZC19–22.
20. Zhang Y, Zhang J, Wang L, Wang K, Svensson P. Effect of transcutaneous electrical nerve stimulation on jaw movement-evoked pain in patients with TMJ disc displacement without reduction and healthy controls. Acta Odontol Scand 2020;78(4):309-320.
21. Özden M, Atalay B, Özden A, Çankaya A, Kolay E, Yıldırım S. Efficacy of dry needling in patients with myofascial temporomandibular disorders related to the masseter muscle. Cranio. 2020;38(5):305-311.
22. Louw W, Reeves K, Lam S, Cheng A, Rabago D. Treatment of Temporomandibular Dysfunction With Hypertonic Dextrose Injection (Prolotherapy): a Randomized Controlled Trial With Long-term Partial Crossover. Mayo Clin Proc. 2019;94(5):820-832.
23. Zhang L, Xu L, Wu D, Yu C, Fan S, Cai B. Effectiveness of exercise therapy versus occlusal splint therapy for the treatment of painful temporomandibular disorders: a systematic review and meta-analysis. Ann Palliat Med. 2021 Jun;10(6):6122–32.
24. Saranya B, Ahmed J, Shenoy N, Ongole R, Sujir N, Natarajan S. Comparison of Transcutaneous Electric Nerve Stimulation (TENS) and Microcurrent Nerve Stimulation (MENS) in the Management of Masticatory Muscle Pain: A Comparative Study. Pain Res Manag. 2019 Nov 23;2019:1–5.
25. Zhang SH, He KX, Lin CJ, Liu XD, Wu L, Chen J, et al. Efficacy of occlusal splints in the treatment of temporomandibular disorders: a systematic review of randomized controlled trials. Acta Odontol Scand. 2020 Nov 16;78(8):580–9.
26. Machado E, Machado P, Wandscher VF, Marchionatti AME, Zanatta FB, Kaizer OB. A systematic review of different substance injection and dry needling for treatment of temporomandibular myofascial pain. Int J Oral Maxillofac Surg. 2018 Nov;47(11):1420–32.
27. Nagori SA, Jose A, Gopalakrishnan V, Roy ID, Chattopadhyay PK, Roychoudhury A. The efficacy of dextrose prolotherapy over placebo for temporomandibular joint hypermobility: A systematic review and meta-analysis. J Oral Rehabil. 2018 Dec;45(12):998–1006.
28. Dym H, Bowler D, Zeidan J. Pharmacologic Treatment for Temporomandibular Disorders. Dent Clin North Am. 2016 Apr;60(2):367–79.
29. Bousnaki M, Bakopoulou A, Koidis P. Platelet-rich plasma for the therapeutic management of temporomandibular joint disorders: a systematic review. Int J Oral Maxillofac Surg. 2018 Feb;47(2):188–98.
30. Machado E, Bonotto D, Cunali PA. Intra-articular injections with corticosteroids and sodium hyaluronate for treating temporomandibular joint disorders: a systematic review. Dental Press J Orthod. 2013 Oct;18(5):128–33.
31. Sit RWS, Reeves KD, Zhong CC, Wong CHL, Wang B, Chung VC ho, et al. Efficacy of hypertonic dextrose injection (prolotherapy) in temporomandibular joint dysfunction: a systematic review and meta-analysis. Sci Rep. 2021 Dec;11(1):1463
32. Lee E, Crowder HR, Tummala N, Goodman JF, Abbott J, Zapanta PE. Temporomandibular disorder treatment algorithm for otolaryngologists. Am J Otolaryngol. 2021 Nov;42(6):103155.

TABLES AND FIGURES:

Scheme 1: Search strategy flow chart

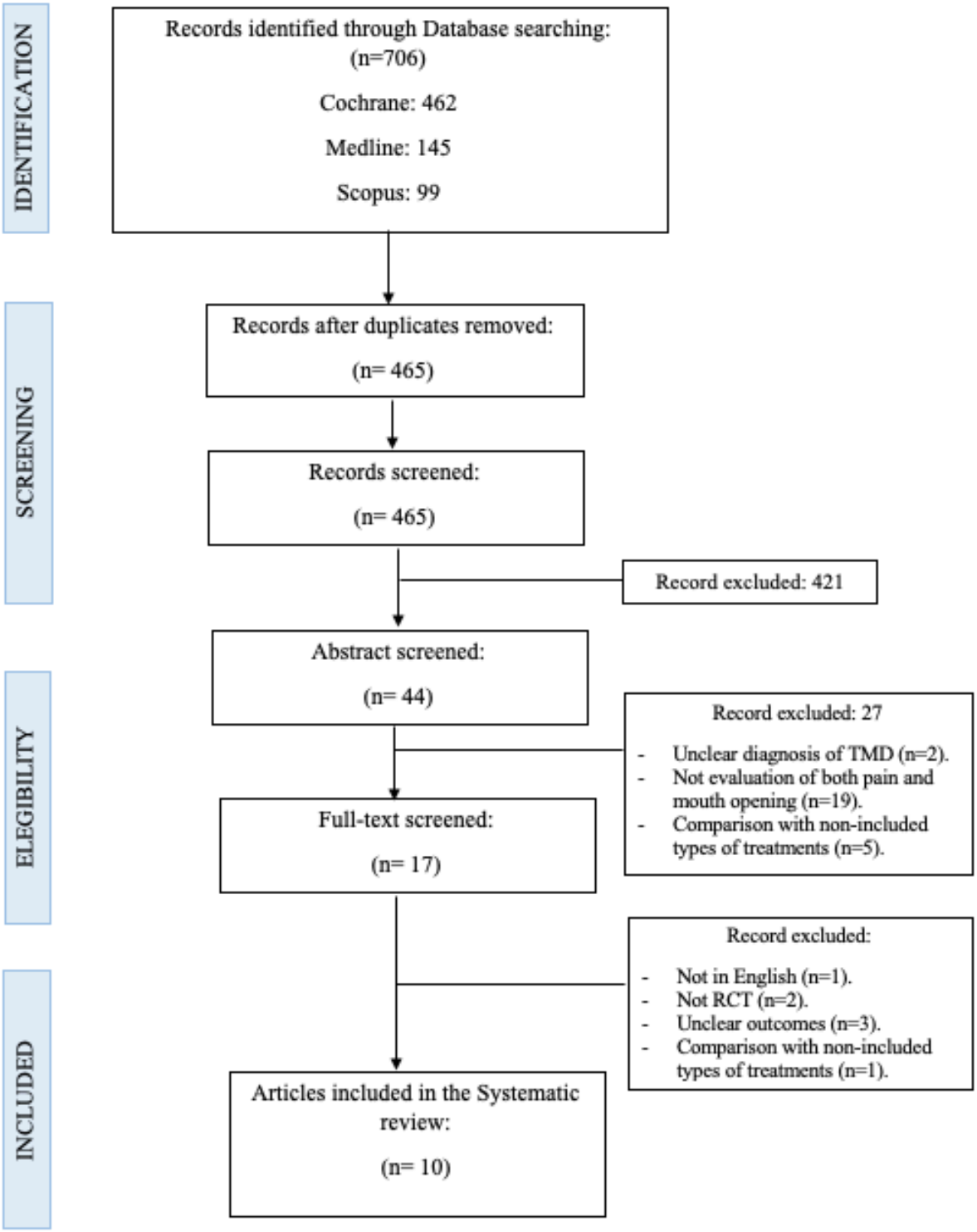


Table 1: Trials' Characteristics

AUTHOR AND YEAR	STUDY DESIGN	Nº OF PATIENTS	AGE OF PATIENTS	MALE-FEMALE RATIO	DIAGNOSTIC CRITERIA	OUTCOME
Ram et al. 2021[13]	Prospective Multicenter Double-blinded RCT	n=120	39.44±10.34.	45.63/ 54.37%.	DC-TMD Axis 1: Local myalgia, myofascial pain, myofascial pain with referral, arthralgia, headache, disc displacement with reduction/ with reduction with intermittent locking/ without reduction with limited opening/ without reduction without limited opening/ degenerative joint disease.	VAS MMO
Sousa et al. 2020[14]	RCT	n=80	43.1 (SD 17.7)	20/80%	DC-TMDs: TMJ arthralgia.	VAS MMO
Delgado et al. 2020[15]	Double-blinded RCT multicenter	n=61	Group1: 44.0 ± 10.5 Group 2: 42.5±12.0	40.98/59.02%	RDC-TMD associated with tinnitus.	NPRS MRM
Priyadarshini et al. 2021[16]	Double-blinded RCT	n=34	Group 1: 31.79 Group 2: 28.35	35.3/64.7%	TMD confirmed by MRI: Wilkes stage II and III TMJ internal derangement.	VAS MMO
Zarate et al. 2020[17]	Double-blinded RCT	n=29	47±18	14/86%	RDC-TMD I (myofascial), II (disc displacement) and III (other joint dysfunctions).	NRS MIO
Harba et al. 2021[18]	Single-blind RCT	n=24	30.58±23.92	NC	Wilkes classification: III (intermediate), IV (late intermediate) & V (late stage).	VAS MMO
Patil et al. 2017[19]	RCT	n=36	Group 1: 34±7.4 Group 2: 32.91±12.57	36.20/ 63.79%	RDC-TMD	VAS MMO
Zhang et al. 2020[20]	Single-blinded RCT	n=40	25-38.	NC	DC-TMD: arthralgia + MRI: TMJ disc displacement without reduction	NRS TOD
Özden et al. 2020[21]	RCT	n=60	18-65.	48/ 52%	RDC-TMD: Group I MTMD	VAS MMO
Louw et al. 2019[22]	Double-blinded RCT	n=44	46±14	16.7/83.3%	RDC-TMD I (myofascial), II (disc displacement) and III (other joint dysfunctions).	NRS MMO

RCT: Randomized controlled trial/ NC: Non-communicated/ RDC-TMD: Research Diagnostic Criteria for temporomandibular disorders/ DC-TMD: Diagnostic criteria for temporomandibular disorders/MTMD: Myofascial temporomandibular disorder/ VAS: Visual analogue scale/ NRS: Numeric Rating Scale/ MMO: Maximum mouth opening/ MRM: Mandibular range of motion/ MIO: Maximum interincisal opening/ TOD: Total oral distance.

Table 2: Subgroups, interventions, follow-up frequency and outcomes results

AUTHOR	SUBGROUPS	INTERVENTIONS	FOLLOW-UP	OUTCOMES RESULTS
Ram et al. 2021[13]	Group 1: Muscle energy technique (n=40).; Group 2: Occlusal splint therapy (n=40).; Group 3: Combined treatment (n=40).; Group 4: Control group (n=40).	○ Muscle energy technique: Post-isometric relaxation & reciprocal inhibition. (3 times/weeks for 4 weeks). ○ Occlusal splint therapy. ○ Muscle energy technique + Occlusal splint therapy. ○ Education for self-management & counseling.	1 week, 2 week, 1 months and after 3 months	Highly significant reduction of pain for groups 1, 2 and 3 as compared to the control group and no significant difference between groups 1, 2, 3. Highly significant improvement of mouth opening for group 1 and 3 as compared to group 2 and 4 and no significant difference between group 1 and 3.
Sousa et al. 2020[14]	Group 1 (Control group): Bite splint therapy (n=20).; Group 2: BS and betamethasone. (n=20); Group 3: BS and sodium hyaluronate (n=20); Group 4: BS and Platelet-rich plasma (n=20).	○ Bite splint with contact in all teeth and canine guidance. ○ Bite splint and pre-auricular injection of 1mL of betamethasone (Diprofofos Depot 7mg/mL). ○ Bite splint and pre-auricular injection of 1L of sodium hyaluronate (Hyalart 10 mg/mL). ○ Bite splint and pre-auricular injection of 2mL of PRP from ulnar vein.	1 week, 1 month, 6 months	All 4 types of treatments showed pain reduction and better mouth opening. Significant pain reduction in all groups treated with injection: lower reduction in group 1 and higher in group 4. Significant increase of pain-free mouth opening in all groups: smaller average rate per week in group 1 and larger in group 4.
Delgado et al. 2020[15]	Group 1 (Control): Exercise + education (n=30); Group 2: Exercise + Education + Manual therapy (n=31).	○ Exercise therapy program (twice/day): Mobility, postural education and motor control exercises of the TMJ, the tongue and the neck; instructions for resting jaw position, neck/head postures. ○ Cervico-mandibular manual therapy group: Manual therapy techniques focusing on the TMJ and the masticatory and cervical musculature.	3 month, 6 months	Greater reduction of pain and mandibular range of motion among group 2.
Priyadarshini et al. 2021[16]	Group 1 (Control): Anterior bite planes (n=17).; Group 2: Anterior bite plane + Prolotherapy (n=17)	○ Anterior bite planes for 12h/ day up to 3 months. ○ Injection of Prolotherapy solution in posterior joint space, anterior disc attachment to the lateral pterygoid muscle, and masseter attachment at day 1, 2 weeks, 6 weeks and 12 weeks: dextrose 50% (0.75ml), lignocaine 2% with adrenaline (1.5ml) and bacteriostatic water (0.75ml)	1 month, 3 months, 6 months, 1 year	Statistically reduction of pain and improvement of mouth opening in group 2.
Zarate et al. 2020[17]	Group 1 (Control): Lidocaine injections (n=15).; Group 2: Lidocaine and Dextrose injections (n=14)	○ Intra-articular injections of Dextrose 20%/lidocaine 0.2% at day one, one month, 2 months and by demand after 3 months. ○ Intra-articular injection of sterile water/lidocaine 0.2% at day one, one month, 2 months and by demand after 3 months.	0,1, 2, 3 months (and by request in the following year).	No significant difference between groups regarding pain reduction. However, group 2 showed a more frequent ≥50% pain improvement group 1. Substantial improvement of MIO for both groups.
Harba et al. 2021[18]	Group 1 (control): HA injection (n=12).; Group 2: HA + PRP injections.	○ 4 intra-articular injection sessions of 1mL of HA /session with 14 days between sessions. ○ Intra-articular injection of 0.5mL of HA + 0.5ml of PRP / session for 4 sessions with a 14-day interval between sessions.	0, 2 weeks, 1 months, 3 months and 6 months.	In both groups: a statistically significant pain reduction after 2 weeks and after 1-month follow-up. In group 1: a significant increase of pain between 3 to 6 months. In both groups: a significant increase of between day 0 and after 2 weeks. However, for group 1, there was a significant decrease of MMO between 1 and 3 months.
Patil et al. 2017[19]	Group 1(Control group): Home exercise (n=18); Group 2: TENS (n=18).	○ Home exercise: education, active and passive jaw opening and closing exercises, isometric jaw exercises, jaw stretching exercises and resistive jaw exercises: twice a day for 4 weeks. ○ TENS therapy during 30mn once a week for a period of 4 consecutive weeks.	0, 1, 2, 3 and 4 weeks.	For both groups: significant decrease of pain between each session, except between 0 to 1 week for group 1. For both groups: significant improvement of MMO between each session but no significant difference between groups.
Zhang et al. 2020[20]	Group 1: Control TENS (n=10); Group 2: Control sTENS (n=10); Group 3: TENS (n=10); Group 4: sTENS (n=10).	○ TENS: Electrical stimulation over both TMJ region 45 min with a green light flashing. ○ sham TENS (sTENS): Same without electrical output.	Before and after intervention.	A significant decrease of NRS pain in group 3 after treatment. No significant difference of TOD before and after TENS intervention but a significant decrease of TOD in the 5^{h} session in group 4.
Özden et al. 2020[21]	Group 1 (Control): Healthy patients without treatment (n=20); Group 2: Superficial dry needling (n=20) Group 3: Deep dry needling (n=20)	○ Superficial dry needling: Intramuscular needling depth up to 5mm in the masseter trigger point during 20mn/weeks over 3 weeks. ○ Deep dry needling: Intramuscular needling depth at least 10mm in the masseter trigger point during 20mn/weeks over 3 weeks.	0, 3 and 6 weeks.	No significant difference between 3 to 6 weeks regarding VAS for pain and MMO for both groups. The trigger point palpation VAS scores in 3rd and 6th weeks were better than the baseline values in both groups.
Louw et al. 2019[22]	Group 1 (Control): 0.2% Lidocaine (n=20). Group 2: Dextrose injection (n=22).	○ Intra-articular injection in the superior joint space of 0.2% lidocaine every month for 2 months. ○ Intra-articular injection in the superior joint space of 20% Dextrose/ 0.2% lidocaine every month for 2 months.	0, 1, 2, 3 months	Higher change in NRS pain in group 2 than group 1 Group 2 showed a higher improvement in MIO than group 1 during the 3 months masked treatment period.

Table 3: CASP Selective criteria

	Ram[13] et al.	Sousa[14] et al.	Delgado de la Serna[15] et al.	Priyadarshini[16] et al.	Zarate[17] et al.	Harba[18] et al.	Patil[19] et al.	Zhang[20] et al.	Özden[21] et al.	Louw[22] et al.
Clearly focused question	+	+	+	+	+	+	+	+	+	+
Randomized	+	+	+	+	+	+	+	+	+	+
Same n° of patients at the beginning & the end	-	?	-	+	-	?	?	+	+	-
Participants, investigators and people analyzing are blinded	-	?	+	+	+	?	-	-	?	+
Study groups similar at the start	?	+	+	-	+	-	+	+	+	-
Same level of care for each group	+	+	+	+	+	+	+	+	-	+
Effects comprehensively reported	+	+	+	+	+	+	+	+	+	+
Reports of the estimate of the intervention or treatment effect	+	+	+	-	+	-	-	-	+	-
The benefits of RCT outweigh the harms and costs	+	+	+	+	+	+	+	+	+	+
Results applicable to our population/ dental clinic	+	+	+	+	+	+	+	+	+	+
Provide greater value to the people in the care than any of existing interventions	+	+	+	+	+	+	+	+	+	+
TOTAL SCORE	8	9	10	9	10	7	9	9	9	8