Official Journal of Erciyes University Faculty of Medicine

DOI: 10.14744/cpr.2024.36855
J Clin Pract Res 2024;46(1):1–10

A Comprehensive Analysis of the Efficacy of Injectable Medications in Relieving Temporomandibular Joint Discomfort: A Systematic Review

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ABSTRACT

Temporomandibular joint (TMJ) discomfort is a prevalent condition affecting a significant portion of the global population, often leading to impaired quality of life and reduced oral functionality. Various treatment modalities have been explored to alleviate TMJ discomfort, with injectable medications emerging as a promising therapeutic approach. This systematic review aims to provide a comprehensive overview of the efficacy of injectable medications in relieving TMJ discomfort. A rigorous search of electronic databases was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The findings are presented in a narrative synthesis, highlighting trends in treatment outcomes and potential complications associated with injectable medications for TMJ discomfort. The Risk-of-bias VISualization (Robvis) and the Mixed Methods Appraisal Tool (MMAT) were used as quality assessment tools. This review synthesizes valuable insights from the scientific literature across multiple electronic databases. A total of 25 articles were selected for inclusion in the study. Most patients investigated had been diagnosed with internal derangement of the TMJ. Various injections, including Sodium Hyaluronate (SH), Autologous Blood Injection (ABI), Platelet-Rich Plasma (PRP), and Corticosteroid (CS), were administered to alleviate pain and discomfort. Most studies administered these injections after arthrocentesis or in combination with other injections. The combination of arthrocentesis with additional injections demonstrated superior outcomes compared to the sole use of a single injection. This review underscores the need for further research to optimize the selection and administration of injectable medications for Temporomandibular disorders management. It also emphasizes the importance of a personalized approach, considering individual patient characteristics and preferences in treatment decision-making.

Keywords: Temporomandibular joint pain relief, injectable medications for TMJ discomfort, medications for TMJ discomfort, TMJ pain, TMJ discomfort.

Cite this article as:
Darwish G. A Comprehensive Analysis of the Efficacy of Injectable Medications in Relieving Temporomandibular Joint Discomfort: A Systematic Review. J Clin Pract Res 2024; 46(1): 1–10.

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Submitted: 05.10.2023
Revised: 24.11.2023
Accepted: 17.01.2024
Available Online: 26.01.2024

Erciyes University Faculty of Medicine Publications - Available online at www.jcpres.com

INTRODUCTION

Temporomandibular joint (TMJ) disorders represent a prevalent medical ailment arising from structural or functional irregularities affecting the masticatory muscles and the TMJ.[1] Mandibular motion within TMJ disorder sufferers can induce pain, persistent inflammatory responses, and discomfort.[2] Consequently, any disruption or dysfunction in this joint can lead to symptoms

that significantly impact an individual's quality of life. The global incidence of TMJ disorder is markedly substantial,[3] experiencing a discernible elevation in adolescence with occurrence rates ranging from from 7% to 30%.[4] The overall occurrence range of TMJ disorders is between 5% and 12%.[5] In contrast to typical chronic pain conditions, TMJ disorders are more frequent in the younger population and are discernibly more prevalent in females than in males, with the prevalence rate exceeding twofold.[5]

The precise etiology of TMJ disorders is poorly understood, but it is thought to result from multifaceted influences.[6] Factors such as psychological stress, anxiety, depression, and anomalous conditions affecting the intra-articular disk are believed to contribute to the pathogenesis of these disorders.[7] Biomechanically, occlusal overloading and parafunctions like bruxism are common contributors. Biologically, elevated estrogen hormone levels influence the TMJ.[6] The assessment of TMJ disorders typically encompasses a comprehensive clinical evaluation, including meticulous palpation of the joint and surrounding muscular structures.[8] For this purpose, diagnostic criteria have been formulated by reputable bodies such as the American Academy of Orofacial Pain and the Research Diagnostic Criteria for Temporomandibular Disorders (TMD) consortium.[8]

The categorization of TMJ disorders spans from the imperceptible articulation of the joint devoid of discomfort (Stage I) to intense joint pain accompanied by significant degenerative osseous alterations (Stage V). This classification system has been a valuable tool in directing therapeutic strategies for managing arthrogenic TMJ disorders.[9] After completing the diagnostic process and reaching a definitive diagnosis, a therapeutic strategy can be formulated to effectively manage the patient's symptoms.

The spectrum of treatment protocols includes interventions varying in invasiveness, from non-invasive modalities to surgical procedures.[10] Non-invasive therapeutic approaches are advisable before embarking on more invasive interventions or enduring solutions of a permanent or semi-permanent nature.[11] Non-invasive therapeutic modalities include physical therapy modalities (iontophoresis and phonophoresis), psychological interventions (cognitive-behavioral therapy), methods of inducing relaxation, and supplementary therapies (acupuncture and hypnosis).[12] Additionally, chiropractic therapy is progressively gaining recognition as a promising therapeutic alternative, characterized by its non-invasive nature.[13] Nevertheless, a prevailing consensus remains elusive regarding the unequivocal superiority of any singular therapeutic intervention in addressing the pain or oral dysfunction associated with TMJ disorders.[12]

While several other treatment modalities have also been proposed for TMJ disorders, injectable medications have gained increasing attention as a potential therapeutic option.[9] Injectable medications offer targeted delivery, allowing for precise administration of therapeutic agents to the affected TMJ area. Proficient in providing prompt alleviation of symptoms, intra-articular injections exhibit satisfactory effects over several months under observation.[14] These injections facilitate the lavage of the TMJ cavity through arthrocentesis, along with the introduction of autogenous preparations such as blood derivatives, cell transplants, or pharmaceutical agents.[15–17] Moreover, hyaluronic acid and corticosteroids are commonly administered via intra-articular injection into the TMJ with dual aims of ameliorating pain and augmenting the range of mandibular abduction.[18] Furthermore, the administration of platelet-rich plasma (PRP) injections has shown supplementary effectiveness when combined with either arthrocentesis or arthroscopy, contributing to the long-term mitigation of pain in individuals afflicted with TMJ disorder.[14,19]

The management of TMJ disorders remains challenging due to their diverse etiological factors and clinical presentations. Current treatment approaches range from conservative measures such as physiotherapy, occlusal splints, and pharmacotherapy to more invasive interventions like surgery. Injectable medications present a promising avenue in TMJ management, offering the potential to directly address local inflammatory processes, muscle spasms, and pain associated with the disorder. Given the growing interest in injectable therapies and the need for evidence-based interventions in TMJ, a systematic review is warranted to synthesize the available evidence on the efficacy of injectable medications. Thus, the comparative evaluation of diverse injectable TMJ materials elucidates their respective impacts on ameliorating TMJ discomfort. This review offers clinicians and researchers a comprehensive understanding of the current knowledge, guiding informed treatment decisions, identifying research gaps, and ultimately contributing to improved patient care and management strategies for TMJ-related discomfort.

MATERIALS AND METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria were followed in conducting this systematic review,[20] as indicated in Figure 1.

Literature Search

The search strategy was established according to the Participants, Intervention, Comparators or Controls, and Outcome (PICO) framework.[21] Population – Patients with TMJ pain or discomfort. Intervention – Injecting medications for the treatment of TMJ. Comparator – Other medications used

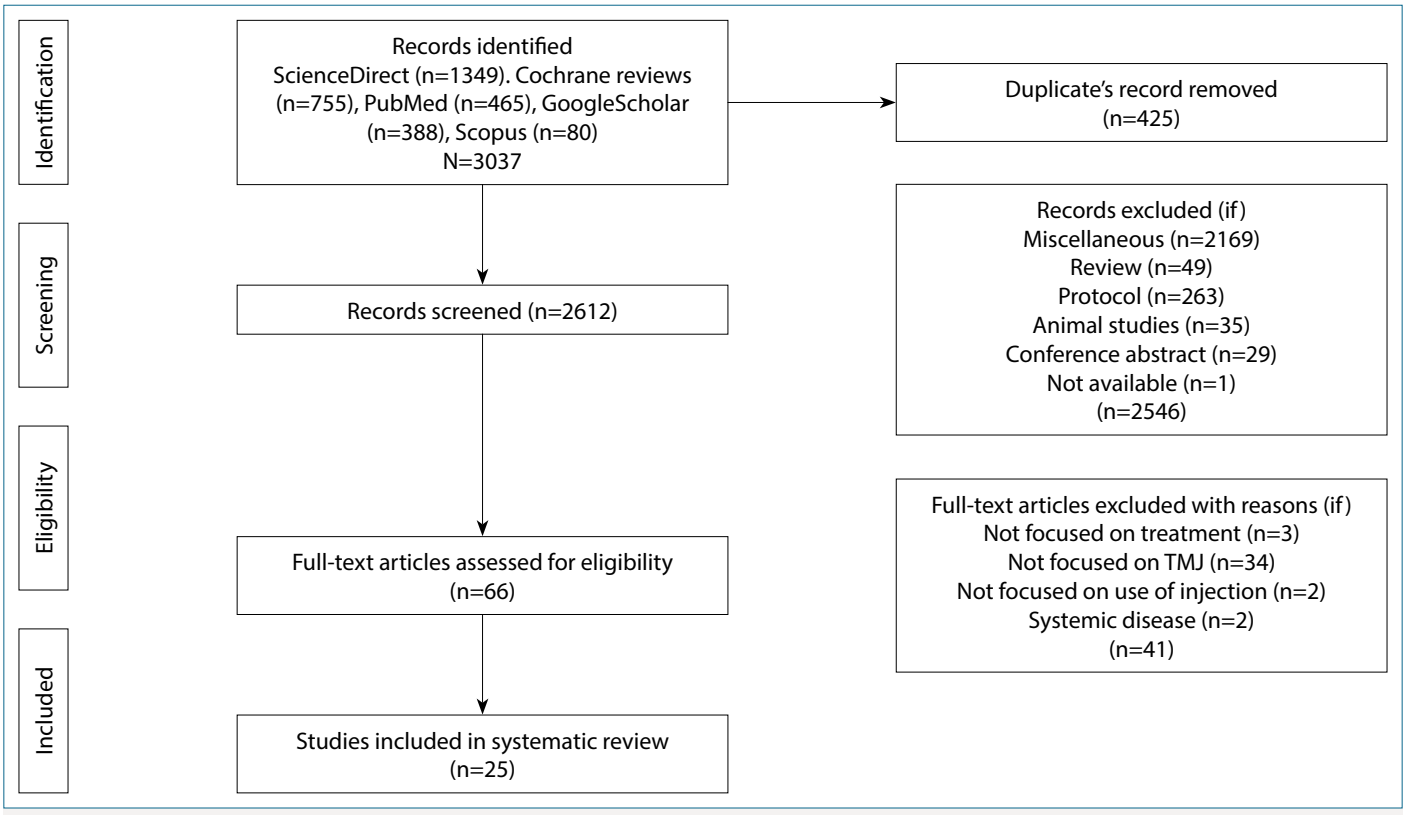

Figure 1. Literature search and screening flowchart.

for the treatment of TMJ. Outcome – Alleviating TMJ pain and discomfort. Various databases were systematically queried to retrieve pertinent research articles, including Science Direct, The Cochrane Library, PubMed, Google Scholar, and Scopus, from January 2013 to September 2023. Diverse keywords such as "Temporomandibular joint pain OR Temporomandibular joint discomfort OR Temporomandibular joint disorder OR TMJ pain OR TMJ disorder" AND "Injections OR Injectable materials OR Injectable Interventions OR Treatment OR Therapies" were used to enhance the comprehensiveness of the search strategy.

Inclusion Criteria

Only studies meeting the following criteria were considered: 1) Original research studies (including retrospective, prospective, cohorts, and randomized controlled trials (RCTs) reporting the efficacy of all TMJ injectable materials. 2) Studies that included both genders and all age groups experiencing TMJ discomfort. 3) Studies published in English. 4) Studies published between 2013 and 2023.

Exclusion Criteria

The following were excluded from the study: 1) Studies that included patients with systemic diseases affecting joint pain. 2) Studies that involved patients with TMJ replacements. 3) Systematic reviews and meta-analysis studies. 4) Studies that used animals as test subjects. 5) Studies not published in English. 6) Studies published before 2013.

Study Selection and Assessment

Original research articles, study titles, and abstracts underwent individual assessment by independent reviewers. Two reviewers independently evaluated the full texts of research papers that met the inclusion criteria. Their findings were deliberated upon to reach a consensus. In cases of discrepancies, a third independent reviewer was consulted, and resolution was achieved through mutual agreement.

Data Extraction

Data extraction was conducted on selected studies that met the predefined inclusion criteria. After screening research articles, a structured data extraction form was employed. This form facilitated the systematic recording of essential information from each study. Two independent reviewers recorded details including authors, publication year, study design, average age, gender, diagnosis, injectable materials used, efficacy, risks, complications, findings, and conclusions.

Quality Assessment

The methodological quality of non-RCTs research articles was assessed using the Mixed Methods Appraisal Tool (MMAT), and quality scores were calculated using the approach described by Charette et al.[22] Studies were classified as either low (scoring ≤3) or high (scoring >3) depending on whether participants answered "yes" (1 point) or "no" (0 points).[23]

For RCTs, the Risk of Bias-2 (RoB-2) tool as part of the Risk-of-bias VISualization (Robvis) was utilized.[24] RoB-2 is categorized into a preset set of bias domains, focusing on various aspects of trial design, conduct, and reporting. Within each domain, a series of "signaling questions" aims to extract information about trial characteristics crucial to the risk of bias.

Data Analysis

The articles selected for the systematic review were compiled utilizing qualitative analysis. The systematic literature review adhered to the PRISMA checklist and outlined a comprehensive article selection procedure.

RESULTS

Literature Search

After conducting an exhaustive examination of the scientific literature through multiple electronic databases, including ScienceDirect (1,349), Cochrane Reviews (755), PubMed (465), Google Scholar (388), and Scopus (80), a noteworthy finding emerged: all research articles had undergone rigorous peer-review processes, resulting in a cumulative total of 3,037 pertinent articles. Subsequently, 425 articles were excluded from this pool. A comprehensive evaluation of 2,612 publications based on their titles and abstracts led to the exclusion of 2,546 articles due to their lack of relevance to our research objectives. The remaining 66 full-text articles underwent thorough scrutiny, with 41 removed for various reasons, as illustrated in Figure 1. Appendix 1 and 2 provide an in-depth analysis of the 25 selected publications, delineating their key attributes.

General Characteristics

The results from various studies conducted in different countries, including Egypt (4), India (4), Saudi Arabia (1), Turkey (7), Spain (1), Estonia (1), Germany (1), France (1), Italy (1), Iraq (2), USA (2), and Syria (1), investigate the effectiveness of different interventions for TMJ-related pain and discomfort. Most studies followed a prospective study design,[25–38] followed by RCTs,[26,39–45] and the least number of articles followed a retrospective study design.[46–48] The maximum number of patients in a study was 102 [41], while the smallest study included 15 patients.[25] Studies included both genders (male and female) as study subjects, as indicated in Appendix 1. Most patients were diagnosed with TMJ internal derangement. Various injections were administrated to relieve pain and discomfort, such as Sodium Hyaluronate (SH), Hyaluronic Acid (HA), Autologous Blood Injection (ABI), PRP, steroids, and Corticosteroids (CS) (Appendix 1). Most of the studies administered injections either after arthrocentesis or in combination. The most commonly diagnosed TMJ conditions included Anterior Disc Displacement with Reduction (ADDR), Anterior Disc Displacement without Reduction (ADDNR), recurrent dislocation, pain, hypermobility, and internal derangement. The most frequently used injection materials were SH, ABI, PRP, HA, betamethasone, fentanyl, Plasma Rich in Growth Factors (PRGF), botulinum toxin, and CS with a 1-2 ml dose for single use (Appendix 1). The studies evaluated a range of outcomes to assess the effectiveness of these interventions. Common outcome measures included maximal mouth opening (MMO), interincisal distance, TMJ pain (measured using a visual analog scale or VAS), muscle tenderness, clicking sounds, occurrence of facial nerve damage, assessing maximum pain during chewing and at rest, quality of life (QoL), Helkimo index, masticatory efficiency, and lateral excursive movements (Appendix 1).

Outcomes

Appendix 2 presents a comprehensive overview of various research studies evaluating treatment (injections) approaches for TMJ, mainly focusing on pain relief, functional improvements, radiological findings, and complications. Appendix 2 summarizes the key findings of these studies, which include various treatment modalities such as arthrocentesis, intra-articular injections, and combined therapies. The studies showed mixed results, suggesting that different approaches yield varying degrees of success in alleviating TMJ-related symptoms, improving joint function, and managing complications. Furthermore, the maximum follow-up duration for evaluating improvements in terms of pain, MMO, and Maximum Incisal Opening (MIO) was 24 months,[45] while the shortest follow-up period was 1.1 months.[29] Most studies used Magnetic Resonance Imaging/Computed Tomography for diagnostic purposes, while a limited number of studies employed radiographic tests to assess improvement.[25,27,42,45] In terms of complications, a limited number of studies reported postoperative swelling and pain.[25] Additionally, transient blepharospasm and paresthesia spreading to the zygomatic arch and preauricular regions were noted,[26] while studies using PRP-based injections reported no complications.[32,42] Overall, arthrocentesis combined with other injections (HA, SH, CS, or PRP) showed better results than a single injection (Appendix 2).

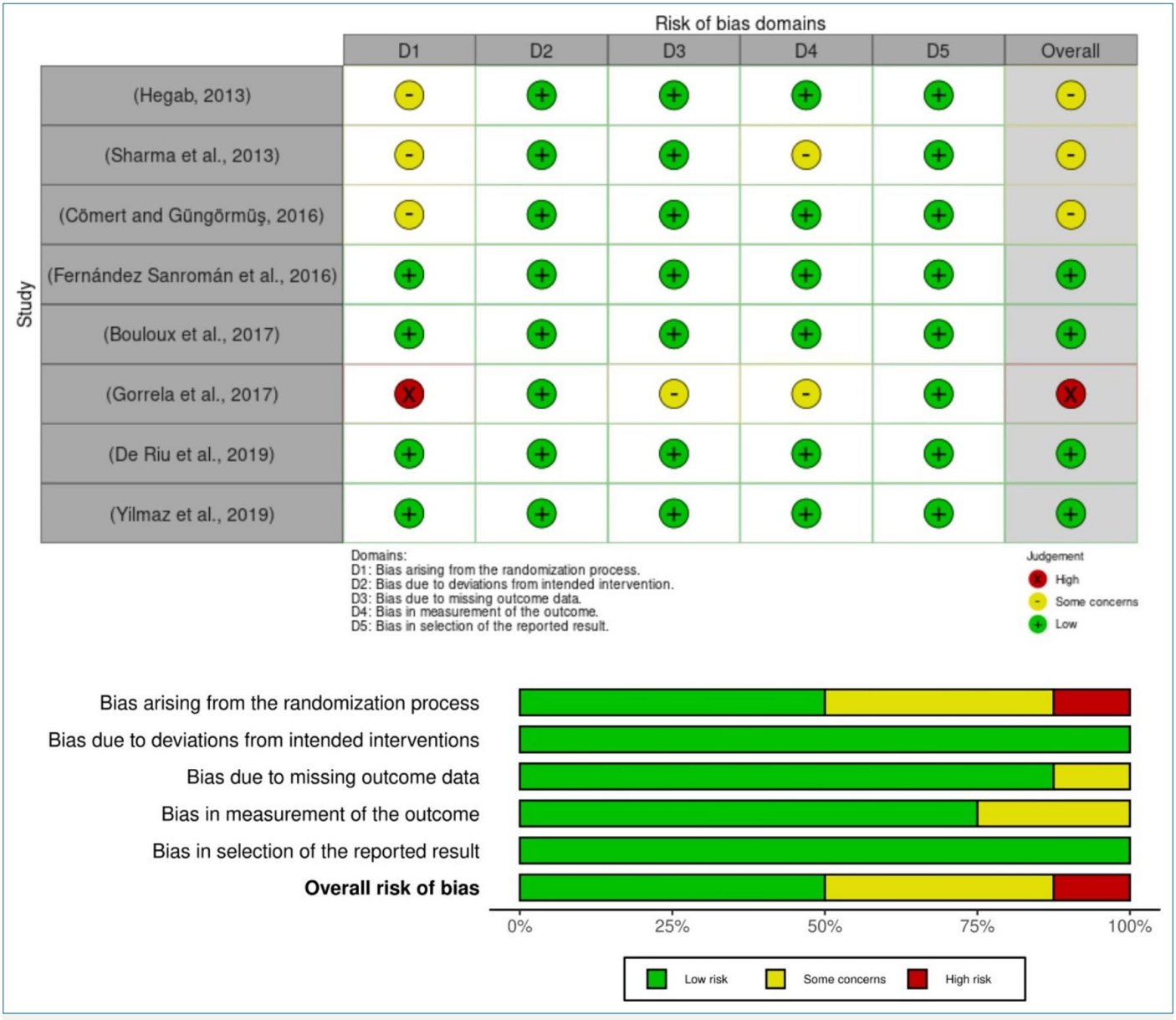

Figure 2. RoB-2 for RCTs.

Quality Assessment for RCTs

The Robvis risk-of-bias tool was employed in this study. The risk of bias assessment framework consisted of five domains: Randomization, Deviation from Intended Intervention, Missing Outcome Data, Measurement of Outcome, and Reporting. The results indicated that four studies exhibited a low risk of bias.[41,42,44,45] Three studies had some concerns in the domain of randomization[26,39,40] and the reporting domain,[40] while a single study had a high risk of bias in the randomization domain and some concerns in the domains of missing outcome data and measurement of outcomes (Fig. 2).[43]

Quality Assessment for Non-RCTs

Prospective and retrospective studies were evaluated through the MMAT, and all the studies were of good quality (Table 1).

DISCUSSION

The TMJ is a complex and crucial component of human craniofacial anatomy, facilitating essential functions such as mastication, speech, and facial expression. It encompasses a range of clinical conditions characterized by pain, dysfunction, and compromised QoL.[50] With the rising prevalence of TMD worldwide and the evolving landscape of treatment

Table 1. Methodological quality assessment of non-randomized studies

Study ID	Study design	MMAT criteria for different studies					Scores
		3.1	3.2	3.3	3.4	3.5	
Elmohandes & Altaweel, 2013	P	Y	Can't tell	Y	N	Y	3
Bayoumi, Al-Sebaei, Mohamed, Al-Yamani, & Makrami, 2014	P	Y	Y	Y	Can't tell	Y	4
Gencer, Özkiriş, Okur, Korkmaz, & Saydam, 2014	P	Y	Y	Y	Can't tell	Can't tell	3
Hancı et al., 2015	P	Y	Y	Y	Can't tell	Y	4
Adil, Abdul Lateef, & Abdulmajed, 2015	P	Y	Y	Y	N	Y	4
Fayed, Elsharrawy, Hamed, & Abd-Allah, 2016	P	Y	Y	Y	N	Y	4
Ivask, Leibur, Akermann, Tamme, & Voog-Oras, 2016	P	Y	Y	Y	N	Y	4
Korkmaz et al., 2016	P	Y	Y	Y	Y	Y	5
Albilia, Herrera-Vizcaíno, Weisleder, Choukroun, & Ghanaati, 2018	P	Y	Y	Y	Can't tell	Y	4
Batifol, Huart, Finiels, Nagot, & Jammet, 2018	R	Y	Y	Y	Y	Y	5
Rao et al., 2019	P	Y	Y	Y	N	Y	4
Marzook, Abdel Razek, Yousef, & Attia, 2020	P	Y	Y	Y	N	Y	4
Yuce & Komerik, 2020	R	Y	Y	Y	N	Y	4
AbdulRazzak, Sadiq, & Jiboon, 2021	P	Y	Y	N	N	Y	3
Torul, Cezairli, & Kahveci, 2021	R	Y	Y	Y	Y	Y	5
Manafikhi, Ataya, & Heshmeh, 2022	P	Y	Y	Y	N	Y	4
Dhiman et al., 2023	P	Y	Y	Y	Y	Y	5

P: Prospective; R: Retrospective; N: No; Y: Yes.

modalities, evaluating injectable therapies is paramount in guiding clinical practice and advancing our understanding of TMJ-related pain management.[51] Injectable medications have emerged as a potential therapeutic avenue for managing TMJ-related discomfort, offering targeted delivery and potentially enhanced efficacy compared to traditional systemic treatments. This systematic review represents a comprehensive investigation into the effectiveness of injectable medications in alleviating TMJ discomfort.

The diagnosis of TMJ internal derangement emerged as a predominant clinical presentation among the patients included in this systematic review. This finding underscores the significance of internal derangement as a primary etiological factor contributing to TMJ discomfort, reaffirming its status as a prevalent and challenging condition encountered in clinical practice.[52] Internal derangement typically encompasses a spectrum of structural and functional abnormalities within the TMJ, including disc displacement, joint effusion, and abnormal condylar positioning, often leading to pain, joint clicking, and restricted jaw mobility.[52,53] These abnormalities disrupt the normal biomechanics of the joint and can result in chronic irritation and inflammation, ultimately causing discomfort and pain.[54] Internal derangement is a prevalent and challenging condition that highlights the intricate relationship between TMJ anatomy and function, making it a key focus in understanding and addressing TMJ discomfort. The high prevalence of this diagnosis in our reviewed population accentuates the need for effective and targeted interventions to mitigate the associated pain and discomfort. Our findings align with other studies; one study revealed that internal derangement was observed in 76 individuals (19%) based on clinical manifestations. Among them, 29 individuals (7%) exhibited reciprocal clicking, while 47 individuals (12%) reported a history of clicking followed by limited mouth opening accompanied by deviation toward the affected side. Notably, those with reciprocal clicking were more likely to experience TMJ pain during mouth opening and encounter restrictions in jaw movement.[55] However, relying solely on clinical examination for an accurate diagnosis can be challenging due to the multifaceted nature of TMJ dysfunction's origins. Therefore, it is advisable to complement clinical assessments with additional imaging modalities to better understand the relationship between the disk and condyle before and after treatment interventions.[56]

Our systematic review observed a spectrum of injectable interventions, each with its unique mechanism of action and therapeutic potential. These interventions included but were not limited to SH, HA, ABI, PRP, various steroids, and CS, as outlined in Appendix 1. The diversity in selecting these injectables underscores the ongoing pursuit of optimal treatment strategies in TMJ pain management. Importantly, it is worth noting that the use of these injections, either after arthrocentesis or in combination with other modalities (SH, HA, PRP, ABI) resulted in better outcomes. This finding reveals an evolving trend towards personalized, multimodal treatment approaches. Another study also revealed that the post-arthrocentesis injection of HA emerges as a notably more effective approach ($p<0.05$) for managing TMD, leading to a reduction in pain levels and enhanced jaw functionality.[36]

Similarly, pain reduction in the group that received arthrocentesis in combination with intra-articular injectable Platelet-Rich Fibrin (i-PRF) injection was observed to be more significant compared to the group that underwent arthrocentesis alone during the 12-month postoperative period (palpation: -6.9±1.2 vs. -5.3±1.3; chewing: -6.9±1.5 vs. -5.1±1.7; jaw movements: -6.9±1.1 vs. -5.1±1.4).[57] Meanwhile, each injection used had its own merits and demerits. For instance, SH injections have gained prominence due to their potential to provide lubrication and cushioning within the TMJ, potentially mitigating the friction and inflammation associated with TMD.[58] ABI and PRP therapies harness the regenerative properties of the patient's blood components, offering a natural and biocompatible approach to pain relief and tissue healing.[59] Moreover, systemic and intra-articular steroids have long been a staple in managing inflammatory conditions, and their use in TMJ injections aims to reduce local inflammation and alleviate pain.[60] It is imperative to consider that the choice of injectable medication should be tailored to individual patient characteristics, including the severity of symptoms, underlying pathology, and response to previous treatments.

Additionally, the potential risks and side effects associated with each injection modality should be weighed against the expected benefits to ensure the safety and well-being of patients. The varying study designs, methodologies, and patient populations in the included studies necessitate a cautious interpretation of the findings. While some injectable medications may exhibit promising results in specific subgroups of patients, the overall quality and strength of evidence for each intervention must be critically assessed. Future research efforts should focus on standardized protocols, larger sample sizes, and long-term follow-up assessments to provide more definitive insights into the comparative efficacy of these injectable therapies in managing TMJ internal derangement.

This systematic review presents valuable insights into the topic but has several limitations, such as the quality of the RCTs potentially affecting the overall reliability of the findings. The review's generalizability may also be limited due to variations in patient populations, treatment modalities, and study designs across the included articles. Furthermore, a longer duration of follow-up than that in some of the selected studies may be required to assess the long-term efficacy and safety of injectable medications for TMJ discomfort. Since the review focuses exclusively on injectable medications, it may provide only a partial overview of all potential treatment options for this condition.

CONCLUSION

This systematic review comprehensively examines the efficacy of injectable medications in alleviating temporomandibular joint discomfort. A thorough analysis of the available literature has identified several promising interventions that show potential to offer relief to individuals suffering from TMJ discomfort. While further research is needed to establish the long-term safety and effectiveness of these injectable treatments, our review underscores the importance of considering these options as part of a comprehensive approach to managing temporomandibular joint disorders. As our understanding of these treatments continues to evolve, healthcare professionals can better tailor their interventions to improve the quality of life for TMJ patients, offering them hope for a more pain-free future.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The author have no conflict of interest to declare.

Financial Disclosure: The author declared that this study has received no financial support.

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