Project Title: “Comparison of Intra-articular Injection of PRGF and Corticosteroid When Used as an Adjunct to Temporomandibular Joint Arthrocentesis: A Blinded Randomized Control Trial”

Principal investigator: Derek Oryniak DMD, BSc, BSc (dent) - PGY-5 OMFS University of Manitoba

Supervising instructor: Dr. Adnan Shah BSc, BDS, MDS (UK), FRACDS (Australia), FDSRCS (Edinburgh) – Program Director Department of Oral and Maxillofacial Surgery, Dr. Gerald Niznick College of Dentistry, University of Manitoba

Co-supervisors: Dr. Reda Elgazzar and Dr. Catherine Dale

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Abstract

Background: Intraarticular pain in dysfunction (IPD) is a notably prevalent condition affecting the temporomandibular joint. Both marcotrauma and microtrauma, from bruxism and parafunctional habits, can lead to internal derangement of the temporomandibular joint disc causing chronic inflammation and pain. Arthrocentesis is a surgical procedure used to reduce this inflammation and return the patient to painless function. Several drugs have been used as an adjunct to arthrocentesis. Research has suggested platelet concentrates may serve as a superior alternative supplement when used in combination with arthrocentesis from the treatment of IPD.

Objectives: To compare the clinical outcomes of platelet-rich in growth factor (PRGF) versus corticosteroid (CS) injections as adjuncts to temporomandibular joint (TMJ) arthrocentesis in patients with predominantly Wilkes stage II–III internal derangement.

Materials and Methods: This single-blinded randomized controlled trial included sixteen participants who underwent standardized unilateral TMJ arthrocentesis. Subjects were randomized to receive either intra-articular triamcinolone (40 mg) or PRGF (2 mL). Clinical outcomes—including maximum interincisal opening (MIO), average daily pain, maximum pain intensity, joint sounds, and muscle tenderness—were recorded preoperatively and at 7, 30, 90, and 180 days postoperatively.

Results: At 6 months, the CS group demonstrated a greater mean improvement in MIO (+7.0 mm) compared with PRGF (–8.6 mm). PRGF resulted in a significant reduction in average daily pain in the early follow-up period, however steroid provided similar early pain reduction, and improved long term pain reduction. Joint sounds and muscle tenderness declined slightly in both groups, with no significant differences between treatments.

Conclusion: Given the small sample size, higher attrition in the PRGF group, and lack of quality-of-life measures, findings should be interpreted with caution. Within these limitations, PRGF did not demonstrate superiority over corticosteroids as an adjunct to TMJ arthrocentesis.

Keywords: Temporomandibular joint disorders, disc displacement, TMJ internal derangement, intra-articular pain and dysfunction, arthrocentesis, platelet-rich growth factor, corticosteroids

Content

1 Introduction

1.1 Temporomandibular Joint Anatomy

The temporomandibular joint (TMJ) is formed by the articulation of the mandibular condyle and the glenoid fossa of the temporal bone. The joint is separated by an avascular, non-innervated articular disc, or meniscus. From an anatomic standpoint, the TMJ is classified as a *diarthrodial joint,* which is a discontinuous articulation of two bones allowing freedom of movement that is dictated by the associated muscles and limited by the associated ligaments.[1] The TMJ is a unique joint in that it provides both hinging and rotational movement. For this reason, it is described as a glinglymoarthrodial joint. Ginglymoid indicates the hinging movement and arthrodial describes a gliding movement type joint.[2,3] The TMJ is also considered a synovial joint. The synovial membrane which lines the joint provides lubrication to the joint as well as nutrition to the avascular articular disc.[3]

The articular segment of the temporal bone, which constitutes the superior aspect of the temporomandibular joint (TMJ), comprises three primary components. The largest of these is the articular fossa, a concave structure that extends from the posterior margin of the articular eminence to the postglenoid tubercle, a ridge separating the fossa from the external acoustic meatus. The surface of the articular fossa is notably thin and may appear translucent when examined in a dry skull specimen. This region is not a significant stress-bearing area of the TMJ, necessitating utmost caution during both arthroscopic and open TMJ surgeries to prevent inadvertent penetration into the middle cranial fossa. In contrast, the articular eminence is a robust segment of bone, serving as the primary functional component of the TMJ. The articular eminence is distinguished from the articular tubercle, a non-articulating process located on the lateral aspect of the zygomatic root of the temporal bone, which acts as an attachment point for collateral ligaments. The third component of the articular surface is the preglenoid plane, a flattened area situated anterior to the articular eminence.[3]

The mandible, a U-shaped bone, articulates with the temporal bone through the articular surfaces of the condyles. The mandibular condyle measures approximately 15 to 20 mm in transverse width and 8 to 10 mm in the anteroposterior dimension. It typically exhibits a

rounded profile mediolaterally and a convex shape anteroposteriorly. A notable feature on its medial aspect, just below the articular surface, is the pterygoid fovea—a prominent depression that serves as the insertion point for the inferior head of the lateral pterygoid muscle. This muscle plays a crucial role in facilitating the protrusion of the mandible during condylar translation.[3]

As with all synovial joints, there are two unique tissues that line the inner aspect of the TMJ. These include articular cartilage and synovium. The space bounded by these two structures is termed the synovial cavity, which is bathed in synovial fluid. The articular surfaces of both the temporal bone and the condyle are covered with dense articular fibrocartilage, a fibrous connective tissue. This fibrocartilage layer has the capacity to regenerate and to remodel under functional stresses. Deep to the fibrocartilage layer, particularly on the condylar head, is a proliferative zone of cells that may develop into either cartilaginous or osseous tissue, based upon functional loads.[3] Articular cartilage is composed of chondrocytes and an intercellular matrix of collagen fibres, water, and a nonfibrous filler material, termed *ground substance*. Chondrocytes are enclosed in otherwise hollow spaces, called *lacunae,* and are arranged in three layers characterized by different cell shapes. There are few blood vessels if any in these areas, so the cartilage receives nourishment primarily by diffusion from the synovial fluid.

The synovial fluid is derived from the synovial membrane which lines the capsular ligaments. Synovial cells appear somewhat undifferentiated and serve both a phagocytic and a secretory role and are thought to be the site of production of hyaluronic acid, a glycosaminoglycan found in synovial fluid.[3] Some sources describe two unique types of synovial cells: Type A synovial cells, which are macrophage-like cells, working to remove debris and Type B synovial cells, which produce hyaluronan, collagen, and fibronectin.[2,4] The synovium is capable of rapid repair and complete regeneration after injury.

The articular disc is composed of dense fibrous connective tissue. As mentioned, it is nonvascualrized and noninnervated in its centre. The annular nature of the disc is what allows it to resist the high pressures occurring during function.[5] This disc is often described as having 3 distinct regions: an anterior band, a central intermediate zone, and a posterior

band (Figure 1). The thickness of each region correlates with the prominence of the eminence, such that the anterior band is the thickest, the intermediate zone is the thinnest, and the posterior band is of intermediate thickness. The intermediate zone is thinnest and is generally the area of maximum function between the mandibular condyle and the temporal bone. The articular disc is attached to the capsular ligament anteriorly, posteriorly, medially, and laterally. Some fibres of the superior head of the lateral pterygoid muscle insert on the disc at its anteromedial aspect and serve to stabilize the disc to the mandibular condyle, via the medial and lateral collateral ligaments, during function.[6]

The posterior aspect of the disc is contiguous with a highly vascularized and highly innervated structure known as the retrodiscal tissues. This region is often responsible for the intra-articular pain experienced by individuals when the disc is anteriorly dislocated, pulling this highly innervated region into the functional region of the joint. Anatomically, the retrodiscal tissues are referred to as the bilaminar zone (superior and inferior retrodiscal laminae). The superior aspect of the retrodiscal tissue contains elastic fibers and is termed the superior retrodiscal lamina, which attaches to the tympanic plate and functions as a restraint to disc displacement in extreme translatory movements.[3,6] The inferior aspect of the retrodiscal tissue, termed the inferior retrodiscal lamina, consists of collagen fibres without elastic tissue and functions to connect the articular disc to the posterior margin of the articular surfaces of the condyle. It is thought to serve as a check ligament to prevent extreme rotation of the disk on the condylar head during rotational movements.[3]

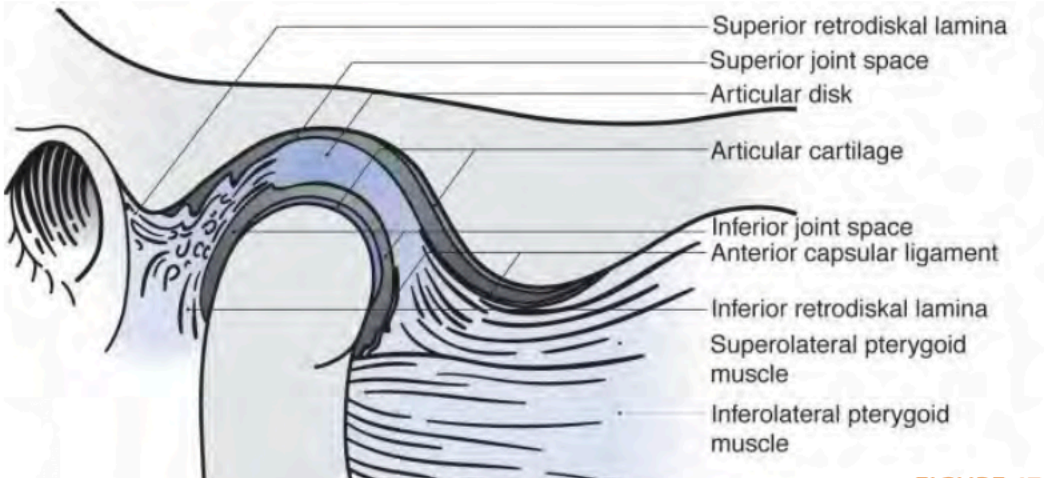


Figure 1. The TMJ (lateral view). Adapted from - Bell WE, editor. *Temporomandibular Disorders: Classification, Diagnosis and Management*. 2nd ed. Chicago: Yearbook Medical; 1986; pp. 16–62.[5]

There are several ligaments of note which facilitate proper functioning of the TMJ. These ligaments are composed of collagen and primarily act to restrain motion of the condyle and the disc. There are five ligaments, three of which are considered functional and two are accessory. The three functional ligaments are the collateral, capsular, and temporomandibular ligaments. These serve as major anatomic components of the joint. The accessory ligaments are the sphenomandibular and stylomandibular ligaments. These are attached to osseous structures away from the joint itself and serve some mild degree of passive restraint on mandibular motion (Figure 2) .[3,4]

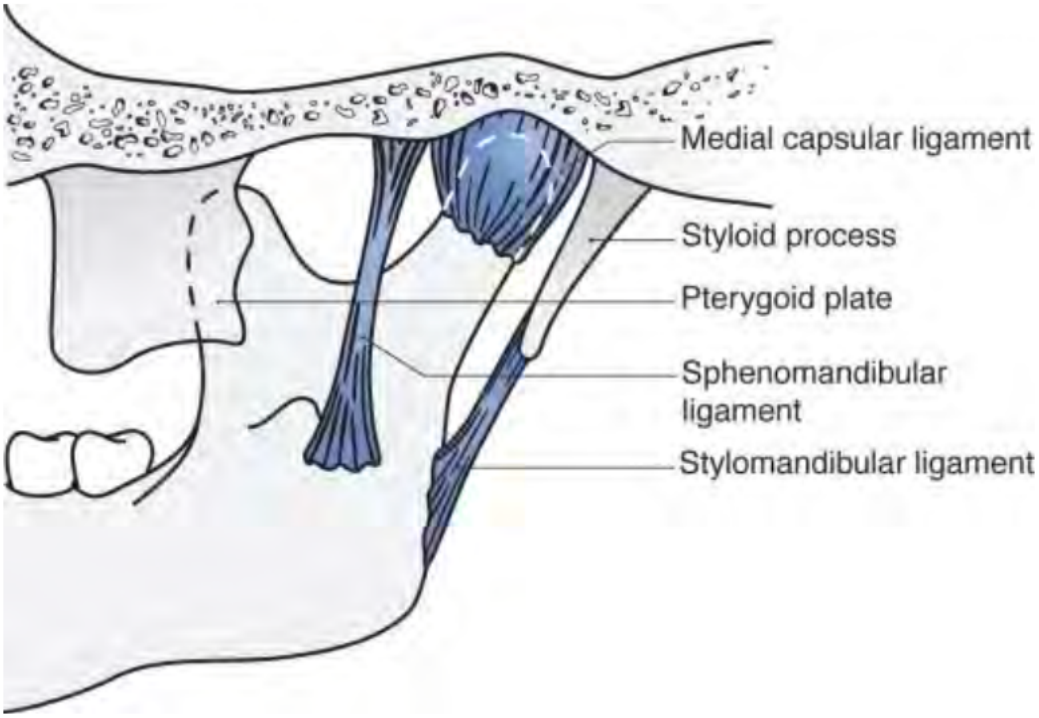


Figure 2. Medial capsular ligament and accessory ligaments of the TMJ. Adapted from - Miloro, Michael ; Ghali, G. E ; Larsen, Peter E ; Waite P. *Peterson's Principles of Oral and Maxillofacial Surgery*. Springer International Publishing AG; 2022. [3]

The vascular supply of the TMJ is characterized by a circumferential distribution, with each vessel within approximately 3 cm contributing one to two branches that nourish the joint tissues. The lateral and ventral regions receive predominant vascularization from the superficial temporal artery and its branches. In contrast, the anterior region is primarily supplied by the deep temporal artery, a branch of the maxillary artery. The medial region is served by the anterior tympanic artery, which can arise from either the maxillary artery or the superficial temporal artery with equal frequency; however, on the right side, it originates from the maxillary artery in 77.8% of cases.[7] Additionally, the middle meningeal artery contributes to this region's blood supply. The retrodiscal tissue is perfused by several branches of the maxillary artery, specifically the anterior tympanic artery (which traverses the intermediate zone), the deep auricular artery, and the middle meningeal arteries. Smaller branches from the superficial temporal artery also play a role in supplying blood to the retrodiscal area.[6]

The innervation of the TMJ is primarily provided by the auriculotemporal nerve, a branch of the trigeminal nerve (cranial nerve V_3). This nerve branches posterior to the joint and ascends laterally and superiorly, encircling the posterior region of the joint. Typically, it comprises two roots that wrap around the middle meningeal artery: the superior and inferior roots.

The superior root divides into several branches, including an anterior auricular branch that supplies the skin over the tragus and adjacent portions of the helix of the ear. Additionally, it gives rise to an articular branch, which provides the main sensory innervation to the posterior aspect of the TMJ, and a superficial temporal branch that innervates the skin over the temple, anastomosing with the facial and zygomaticotemporal nerves. Furthermore, an external auditory meatus branch innervates the skin of the meatus and the tympanic membrane. The inferior root features a prominent branch known as the parotid branch, which delivers secretomotor innervation to the parotid gland and provides vasomotor fibres that innervate the gland's vasculature.[8] There is additional innervation to the TMJ from two other branches of the trigeminal nerve, the deep temporal and the masseteric nerve.[8]

Numerous muscles are involved in the movement of the mandible, with the four primary muscles of mastication being the masseter, temporalis, medial pterygoid, and lateral pterygoid—collectively referred to as the supramandibular muscles. All four of these muscles receive innervation from specific branches of the trigeminal nerve. The masseter and medial pterygoid muscles primarily function to elevate and protrude the mandible, while the temporalis muscle elevates and retracts it. The lateral pterygoid is responsible for depressing and protruding the mandible (Table 1). In addition to these, there are eight supplementary muscles that contribute to mandibular movement, all classified as inframandibular. These can be divided into two categories: the suprahyoid and infrahyoid muscles. The suprahyoid group includes the digastric, geniohyoid, mylohyoid, and stylohyoid muscles, which are positioned between the mandible and the hyoid bone. These muscles function to elevate the hyoid bone when the mandible is fixed by the supramandibular muscles or to depress the mandible when the hyoid bone is stabilized by

the infrahyoids. The infrahyoid group, consisting of the sternohyoid, omohyoid, sternothyroid, and thyrohyoid muscles, connects the hyoid bone superiorly to the sternum, clavicle, and scapula inferiorly. This group can either depress the hyoid bone or maintain its position relative to the trunk during mandibular opening movements.[3]

Table 1. Muscles of mastication and resultant jaw movement. Adapted from Miloro, Michael; Ghali, G. E; Larsen, Peter E; Waite P. *Peterson's Principles of Oral and Maxillofacial Surgery*. Springer International Publishing AG; 2022. [3]

Muscle of mastication	Resultant Jaw Movement
Medial pterygoid	Protrusion, closure
Lateral pterygoid (inferior head)	Protrusion, opening (contralateral)
Lateral pterygoid (superior head)	Retrusion, closure (ipsilateral)
Masseter (superficial layer)	Protrusion, closure (contralateral)
Masseter (deep layer)	Retrusion, closure (ipsilateral)
Temporalis (anterior portion)	Closure
Temporalis (posterior portion)	Retrusion, closure (ipsilateral)

1.2 Intra-articular pain and dysfunction

The term intra-articular pain and dysfunction (IPD) was recently adopted by the AAOMS in their 2022 position paper on the contemporary management of temporomandibular joint dysfunction.[10] It has been recommended the term IPD be used in replacement of older terms such as "internal derangement" and "anterior disc displacement" which specify a mechanical finding that alone may not be causative or associated with signs or symptoms. For the purpose of this paper, the phrase "internal derangement" will be utilized, with clarification where needed, as much of the research on this topic used this term when discussing TMJ dysfunction. It will be explained, that disc displacement is not the only cause of TMJ pain and dysfunction, and many patients do not experience issues from a disc that is

anteriorly displaced, and self-reducing. Other causes of pain such as synovitis and capsular impingement must also be considered and are amenable to arthroscopic intervention.[10]

The term “internal derangement” was utilized for over a hundred years in surgical and orthopedic literature to refer to issues that disrupt normal joint operation. In the knee, this term generally encompasses a torn, ruptured, or otherwise damaged meniscus, as well as partial or complete tears of the cruciate ligaments, with or without damage to the knee's capsular ligament. These conditions can lead to persistent or intermittent symptoms, including pain, instability, or unusual movement patterns.[11] Alterations in the disc, condyle-fossa relationships in the TMJ were suspected as early as 1887 by Sir Astley Cooper and published by Annandale in the Lancet article “ On displacement of the inter-articular cartilage of the lower jaw, and its treatment by operation”.[12]

The term internal derangement was then adopted and used to describe disturbances between the articulating components of the TMJ, alluding to damage to the internal structures and dysfunction of the joint associated with changes in the position of the disc.[13]

In the literature on TMJ disorders, the term had come to be closely associated with disc displacement. During the 1970s and 1980s, TMJ internal derangement was viewed primarily as a mechanical issue, prompting efforts to reposition or replace the disc. In 1979, McCarty and Farrar emphasized the significance of disc displacement as a key disorder of the TMJ.[13]

A frequently conducted surgical intervention involved the repositioning of the intra-articular disc. In cases where the disc was perforated or irreparable, discectomy was often necessary. A variety of materials and tissues were utilized for disc replacement, including cartilage, dermis, muscle fascia, fat, silastic, and Proplast-Teflon. However, the use of Proplast-Teflon led to significant damage to the articular surfaces, primarily due to adverse reactions from foreign body giant cells.[14]

Research in both clinical and basic sciences has elucidated that internal derangement, now best described as IPD, manifests as a spectrum of biomechanical failures within joint tissues, attributable to a range of underlying causes. The Wilkes staging system (Table 2) effectively categorizes the extent of joint damage associated with internal derangement, although it does not specify the precise etiological factors leading to tissue failure.[15]

Nonetheless, this classification remains instrumental in articulating the severity of joint conditions and guiding therapeutic interventions.

Table 2. Wilkes classification of Temporomandibular joint internal derangement. Adapted from - Miloro, Michael ; Ghali, G. E ; Larsen, Peter E ; Waite P. *Peterson's Principles of Oral and Maxillofacial Surgery*. Springer International Publishing AG; 2022. [3]

Stage	Clinical and anatomic findings
Stage I (Early)	Painless clicking Anterior disc displacement with reduction
Stage II (Early intermediate)	Clicking with intermittent pain and locking **Anterior disc displacement with reduction**
Stage III (Intermediate)	Pain, joint tenderness, frequent and prolonged locking, restricted motion, No degenerative changes **Anterior disc displacement with or without reduction**
Stage IV (Intermediate- late)	Chronic pain, restricted motion, no clicking, degenerative bony changes Adhesions Anterior disc displacement without reduction
Stage V (Late)	Variable pain, painful function, reduced function, crepitus, advanced degenerative bony changes, gross disc deformity and/or perforation Advanced adhesions. Anterior disc displacement without reduction

IPD of the TMJ is a notably prevalent condition. Farrar estimated that as many as 25% of individuals may experience IPD. Epidemiological studies indicate that TMJ clicking can be observed in up to 31% of the population, while crepitus is detectable in approximately 40% upon auscultation, with a higher incidence observed in women.[16]

Investigations into the significance of disc displacement and position in symptomatic patients have raised questions, particularly since MRI studies have revealed disc displacement in 32–38% of asymptomatic individuals and volunteers. As mentioned, it is

now understood that an abnormally positioned disc is not the primary source of pain and dysfunction for many patients, as most individuals with displaced discs remain asymptomatic due to their capacity for adaptation.[17]

IPD serves as both an endpoint and a manifestation of a process characterized by damage to the articular tissues and biomechanical failure, necessitating the identification of specific underlying causes for effective treatment. The primary etiological categories contributing to IPD include:

- **Macrotrauma**: Significant impact to the jaw, such as from sports injuries or assaults.
- **Microtrauma**: Parafunctional habits, including clenching and bruxism.
- **Systemic arthropathy**: Conditions such as rheumatoid arthritis, systemic lupus erythematosus (SLE), psoriatic arthritis, HLA-B27 related disorders, and infections.

An alternative perspective on etiology delineates:

- **A normal joint subjected to excessive load (due to trauma or parafunction).**
- **An abnormal joint subjected to normal load (as seen in conditions like rheumatoid arthritis, SLE, or osteochondromatosis).**[18]

Most patients typically fall into the category of a normal joint experiencing overload, predominantly due to parafunctional habits like clenching or bruxism, whether during the day or at night. Historically, occlusion was regarded as a primary etiological factor however, this notion has been challenged and refuted by contemporary evidence-based literature.[18]

As reviewed, the articular disc, interposed between the mandibular condyle and the articular eminence of the temporal bone, is a fibrocartilaginous structure characterized by its biconcave elliptical form. This disc exhibits a thicker anterior and posterior band, with a comparatively thinner intermediate zone. From a lateral perspective in the closed-mouth position—when the condyle is properly seated within the glenoid fossa—the posterior band is conventionally aligned at the 12 o'clock position relative to the center of the condyle. As the condyle undergoes both rotation and translation forward beneath the disc during the process of mouth opening, the disc ascends to a position above the condyle, a phenomenon

known as “roofing.” Disc displacement occurs most commonly in the anterior or anteromedial direction, which is the most common direction of displacement followed by lateral and rarely posterior displacement accounting for only 0.7% of displacements.[19] Disc displacement is said to be “*reducing*” when the disc returns to normal position on complete mouth opening, or “*non-reducing*” when the mandibular condyle is impeded from fully translating, by an anteriorly dislocated disc (Figure 4).

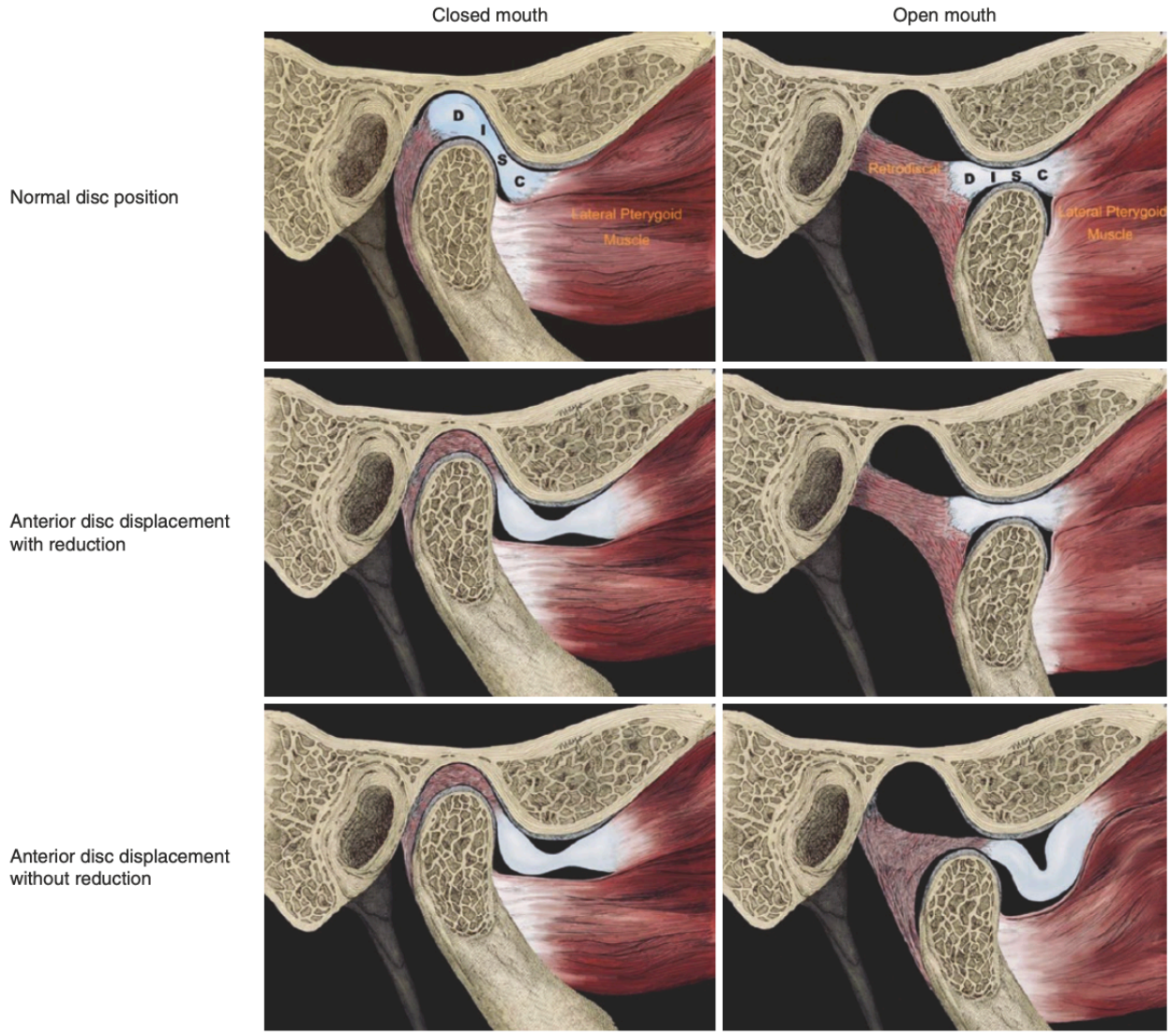
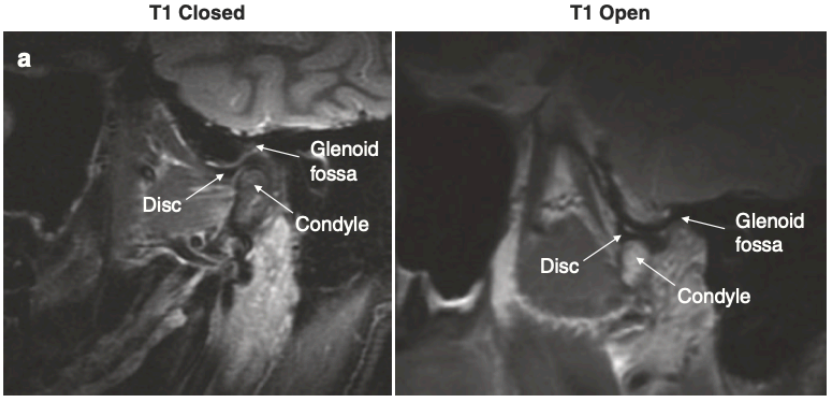


Figure 4. Normal and displaced disc positions, with and without reduction. Adapted from - Warburton G. Internal Derangements of the Temporomandibular Joint. In: Bonanthaya, Krishnamurthy; Panneerselvam, Elavenil; Manuel, Suvy; Kumar VV. et al., ed. *Oral and Maxillofacial Surgery for the Clinician*. Springer International Publishing AG; 2021:1361-1380.[18]

Radiographic assessment of the TMJ serves as a valuable adjunct to the clinician's clinical examination, aiding in the identification of any significant anatomical irregularities. While plain radiographs and computed tomography (CT) scans are effective for assessing bony changes, magnetic resonance imaging (MRI) is particularly well-suited for evaluating disc position and displacement, boasting a diagnostic accuracy of at least 90%. MRI should be performed using both T1- and T2-weighted images in both the open and closed mouth positions. Additional imaging sequences, such as fat suppression or Short Tau Inversion Recovery (STIR), are often advantageous for detecting edema in fat-containing tissues, which can be instrumental in evaluating edema within the cancellous bone of the condylar head.[20]

Through MRI, one can comprehensively assess the bone of the condyle, fossa, and eminence, looking for signs of sclerosis, erosions, flattening, osteophytes, and disruptions in cortical continuity. The imaging allows for detailed examination of the disc, including its position, density, shape, size, and continuity in cases of perforation. Effusions are readily identifiable on T2 sequences, and the integrity of the joint space can also be evaluated. Sagittal images in both the closed and open mouth positions are critical for determining whether the disc is displaced and whether it reduces upon opening (Figure 5).[18,20]



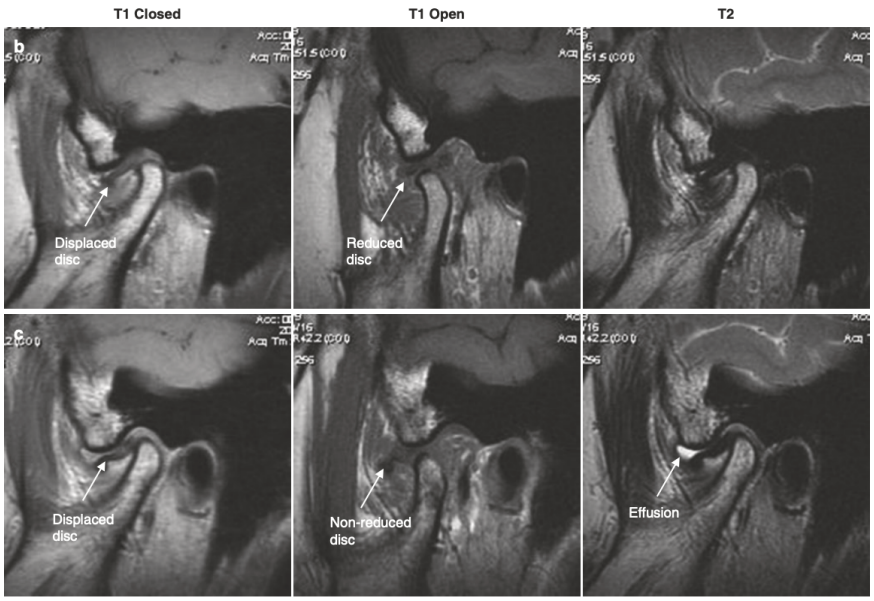


Figure 5. MRI scan—T1 and T2 images in closed and open mouth positions. (**a**) Normal disc position. (**b**) Anterior disc displacement with reduction. (**c**) Anterior disc displacement without reduction and superior joint space effusion. Adapted from - Warburton G. Internal Derangements of the Temporomandibular Joint. In: Bonanthaya, Krishnamurthy; Panneerselvam, Elavenil; Manuel, Suvy; Kumar VV. et al., ed. *Oral and Maxillofacial Surgery for the Clinician*. Springer International Publishing AG; 2021:1361-1380.[18]

Treatment for IPD can be categorized into nonsurgical and surgical options, yet the overarching goals of both approaches remain consistent:

- Decrease joint overload
- Alleviate pain
- Reduce inflammation
- Enhance range of motion
- Restore functional capacity
- Identify and manage causative factors

By focusing on these objectives, clinicians can develop a comprehensive treatment plan tailored to the individual needs of the patient.[18] Clinical research into the natural progression of TMJ IPD indicates that many patients experience improvement without any intervention. On average, symptom resolution typically occurs within one year; however, this timeframe can vary significantly among individuals. About 25–33% of patients do not improve. Older patients and those with MRI evidence of more advanced disease

(osteoarthritis and advanced internal derangement) are at higher risk for not improving spontaneously.[21]

Nonsurgical management options for TMJ disorders encompass several evidence-based approaches. Patient education is fundamental in fostering understanding of the condition and promoting self-management strategies. Dietary modifications, specifically the adoption of a soft diet, can alleviate mechanical stress on the joint. The utilization of occlusal appliances or orthotic devices may help in stabilizing occlusion and reducing symptoms.[18] Increasing awareness of parafunctional habits is crucial, as these behaviours can exacerbate TMJ disorders. Biofeedback techniques can assist patients in gaining better control over muscle tension and minimizing discomfort. Pharmacological interventions, including nonsteroidal anti-inflammatory drugs (NSAIDs) and muscle relaxants, can provide symptomatic relief. The application of botulinum toxin has also been shown as a therapeutic option for reducing muscle hyperactivity. And lastly, physical therapy is a valuable component of a comprehensive treatment plan, aiming to enhance function and alleviate pain through targeted exercises and modalities.[18]

Costen, an otolaryngologist, was the first to propose a connection between occlusion, TMJ disorders, and ear symptoms in 1934, based on his observations of 11 patients.[22] This foundational idea eventually led to the development of orthotics and occlusal therapies for the treatment of TMJ disorders during the 1940s and 1950s. However, a significant paradigm shift has since occurred, as traditional dental and skeletal etiological theories have been increasingly challenged and refuted by global research. This has paved the way for a biopsychosocial model that incorporates aspects of orthopedics, pain physiology, and behavioural factors. Consequently, the conceptual framework for the use of occlusal appliances and orthotics has evolved considerably. Initially, these devices were designed with the belief that they could facilitate occlusal disengagement, relax jaw musculature, restore the vertical dimension of occlusion, relieve joint stress, or reposition the condyle and/or disc. Today, while these appliances are still often referred to as deprogrammers or jaw-repositioning devices, their application is increasingly understood within a broader

context aimed at establishing optimal craniomandibular relationships, alleviating pain, and restoring functional capabilities.

Most patients with temporomandibular disorders (TMD)—approximately 90%—will experience symptom resolution either spontaneously or through nonsurgical interventions.[23] This resolution can be attributed to the inherent adaptive capacity of the TMJ. As stated, internal derangement is commonly identified via MRI in 32–38% of asymptomatic individuals, highlighting the TMJ's ability to accommodate disc displacement in most cases. For patients with IPD who do not demonstrate this adaptive response, surgical intervention may be necessary. Leading authors such as Warburton advocate for a structured surgical pyramid algorithm, typically starting with arthrocentesis or arthroscopy, barring specific contraindications such as ankylosis.[18] As no surgical procedure guarantees a total success rate, patients who do not achieve satisfactory outcomes from the initial procedure (phase 1) may progress to a subsequent surgical intervention (phase 2), with the specifics of this second procedure guided by the arthroscopic findings from the first phase (Figure 6).[18]

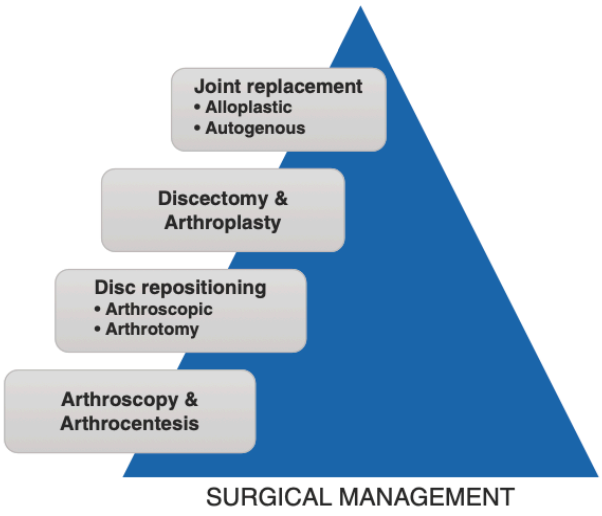


Figure 6. Management of TMD surgical pyramid. Adapted from - Warburton G. Internal Derangements of the Temporomandibular Joint. In: Bonanthaya, Krishnamurthy; Panneerselvam, Elavenil; Manuel, Suvy; Kumar VV. et al., ed. *Oral and Maxillofacial Surgery for the Clinician*. Springer International Publishing AG; 2021:1361-1380.[18]

1.3 Arthrocentesis

Arthrocentesis of the TMJ has been described as a proven treatment modality, filling the gap between conservative and open operational approaches to IPD. Arthrocentesis is a minimally invasive procedure and was introduced following the recognition of the success of simple arthroscopy. Arthrocentesis of the TMJ was first described in 1987 by Murakami, utilizing a single needle pumping technique to achieve hydraulic distention of the upper joint space. Nitzan and Dolwick later refined this approach by employing a two-needle method.[24,25] This technique involves the lysis and lavage of the upper joint space, using an inflow needle, an outflow needle, and at least 300 mL of Lactated Ringer's solution. The lysis is facilitated by hydraulic distention, while the lavage removes inflammatory mediators, cytokines, and debris. Through these processes, adhesions are separated, and inflammatory substances and debris are cleared. Numerous studies have since reported the general success rates for arthrocentesis in managing IPD to be between 70% and 95%.

Studies examining the pre- and postoperative imaging of patients treated with arthroscopic lysis and lavage have shown that improvements in disc position are rare, yet possible. Some researchers have assessed changes in disc position after hydraulic distention and arthrocentesis through clinical examination. Others have evaluated disc position using MRI before and after these procedures, finding no change in preoperative MRI diagnoses. More recent MRI studies, however, suggest the possibility of changes in disc position following arthrocentesis treatment.[26] Clinical trials have demonstrated that arthrocentesis can be effective in correcting a closed lock (anterior disc dislocation without reduction), however this is much more likely in acute patients (often described as closed lock of 4 weeks of less), than in chronic patients.[26]

While high success rates are often quoted, diverse results have emerged due to the use of different fluids (such as saline or Ringer's solution) with varying lavage volumes, administered at different intervals (ranging from a single procedure to multiple sessions until the final follow-up). Additionally, many protocols have incorporated intra-articular drug deposition (IDD) as either an adjunct therapy or a substitute for arthrocentesis, leading to

intracapsular injections becoming standalone procedures. Various IDD options have been explored, with hyaluronic sodium, corticosteroids, and recently platelet concentrates.
A recent systemic review attempted to organize the heterogenous body of literature. Their review found that according to existing literature, arthrocentesis, whether performed via the double-needle technique or the single-puncture method, is a clinically validated treatment that significantly reduces pain and increases the maximum width of mouth opening in cases of disc displacement with or without reduction. The additional intra-articular application of medications, such as hyaluronic acid, corticosteroid, or platelet rich plasma (PRP), does not enhance the outcomes of arthrocentesis. However, using intra-articular injections without arthrocentesis is less effective; it provides comparable maximum mouth opening but reduces pain less effectively. This review found that the type of fluid used for lavage (Ringer's lactate or saline) and its total volume are not critical factors.[27] Recent clinical trials on this topic will be reviewed in the discussion of this thesis, in comparison to the results of the current study.

1.4 Inflammation and anti-inflammatory mechanism of steroids

Inflammation is a biological response of the body's immune system to harmful stimuli, such as pathogens, damaged cells, or irritants. It is a protective mechanism aimed at removing these threats and initiating the healing process. Inflammation can be acute (short-term) or chronic (long-term), and while it is essential for recovery, persistent inflammation can lead to various diseases.[28] The inflammatory cascade is a complex series of events that occur during inflammation. It involves various cells, signaling molecules, and pathways. A simplified overview of the key steps involved can be described as:

1. Recognition of Injury or Pathogen: Damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs) are recognized by receptors on immune cells (such as macrophages and dendritic cells).
2. Release of Inflammatory Mediators: Upon recognition, immune cells release signaling molecules such as cytokines (e.g. interleukins, tumour necrosis factor-

alpha) and chemokines. These mediators facilitate communication between cells and attract other immune cells to the site of injury.

3. Vasodilation and Increased Permeability: Inflammatory mediators cause blood vessels to dilate (vasodilation) and become more permeable. This leads to increased blood flow which allows immune cells, proteins, and nutrients to reach the affected tissue.
4. Recruitment of Immune Cells: Neutrophils are usually the first responders, followed by monocytes (which can differentiate into macrophages). These cells migrate to the site of inflammation guided by chemokines.
5. Phagocytosis and Clearance: Immune cells engulf and destroy pathogens and debris through a process called phagocytosis. Macrophages play a crucial role in clearing up dead cells and pathogens.
6. Resolution of Inflammation: Once the threat is eliminated, anti-inflammatory cytokines and specialized pro-resolving mediators (SPMs) promote the resolution of inflammation. This includes apoptosis of immune cells and tissue repair processes.
7. Tissue Repair and Healing: Growth factors and other signaling molecules contribute to tissue regeneration and repair. This phase aims to restore homeostasis and normal tissue function.

While inflammation is a vital protective response, dysregulation can lead to chronic inflammatory diseases such as cardiovascular diseases, autoimmune disorders, and as it relates to the TMJ, arthritis. Understanding the inflammatory cascade is critical for developing treatments targeting these conditions.

For many decades it has been known that there are numerous inflammatory mediators released by the body which act in cascading fashion. These include amines, such as histamine and 5-hydroxytryptamine, short peptides such as bradykinins, long peptides such as interleukin-1, lipids such as prostaglandins (PGs) and leukotrienes (LTs), enzymes released from migrating cells, and other complement mediators. All these respective mediators can be triggered by different events and contribute to an inflammatory process.[28]

Histamines are organic compounds that play significant roles in various physiological processes within the body, particularly in the immune response, regulation of stomach acid, and neurotransmission. They are synthesized from the amino acid histidine through the action of the enzyme histidine decarboxylase and are stored in granules within mast cells and basophils.[29] Histamines are released in response to various stimuli, such as allergens, injury, or certain drugs. Tissue damage can also cause histamine release as part of the inflammatory response.

Histamines exert their effects by binding to specific receptors on target cells, with four main types identified: H1, H2, H3, and H4 receptors. H4 receptors are involved in immune system regulation and inflammatory responses.[30] The physiological effects of histamines vary depending on the receptor activated. They cause vasodilation, which increases blood flow to the affected area, resulting in redness and heat. Histamines also increase the permeability of blood vessel walls, allowing immune cells and proteins to enter tissues, leading to swelling (edema). Overall, histamines play a crucial role in the immune response, contributing to allergy symptoms and inflammation.[30]

Bradykinins are small peptides that play a significant role in the body's inflammatory response. They are part of the kinin system, which involves a series of proteins that help regulate blood pressure, fluid balance, and inflammation.[31] They are formed from the cleavage of kininogen, a precursor protein, by specific enzymes known as kallikreins. This process typically occurs in response to tissue damage or inflammation. Bradykinins are important mediators in the inflammatory process, facilitating vasodilation, increasing vascular permeability, inducing pain, and recruiting immune cells. Excessive bradykinin activity can contribute to chronic inflammation and pain, highlighting their dual role in health and disease.[28,32]

Prostaglandins are a group of lipid compounds derived from fatty acids, playing essential roles in various physiological processes throughout the body. Classified as eicosanoids, these signaling molecules are synthesized from arachidonic acid, a fatty acid found in cell membrane phospholipids, through the action of cyclooxygenase (COX) enzymes. Prostaglandins are key mediators of the inflammatory response, promoting vasodilation,

increasing blood flow to affected tissues, and enhancing blood vessel permeability, which contributes to the redness, heat, swelling, and pain associated with inflammation. Certain prostaglandins also sensitize nerve endings to pain stimuli, making them important in the experience of pain, particularly in response to injury and infection.[28,33]

In addition to their role in inflammation, prostaglandins influence blood flow by regulating the contraction and relaxation of smooth muscle in blood vessels, thereby affecting blood pressure. They are vital for gastrointestinal function, helping protect the stomach lining by promoting mucus production and regulating gastric acid secretion, as well as aiding in intestinal motility. In the female reproductive system, prostaglandins facilitate ovulation, menstruation, and labor by inducing uterine contractions during childbirth. Furthermore, they play a role in kidney function by regulating renal blood flow and glomerular filtration rate, contributing to fluid and electrolyte balance.

Due to their significant roles, prostaglandins are targets for various medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs), which work by inhibiting COX enzymes and reducing prostaglandin synthesis, leading to decreased pain and inflammation. Understanding prostaglandins and their functions is essential for managing inflammatory conditions, pain, and various physiological processes in the body.[33]

Thromboxane A2 and prostacyclin were discovered by Samuelsson in 1975. Thromboxane A2 (TXA_2) is a potent lipid compound that belongs to the family of eicosanoids, which are signalling molecules derived from fatty acids. Specifically, TXA_2 is synthesized from arachidonic acid through the action of cyclooxygenase enzymes (COX), particularly COX-1. It is primarily produced by activated platelets and plays a critical role in hemostasis and the regulation of vascular tone. Soon after the discovery of TXA_2, another prostaglandin known as prostacyclin was discovered that shows the opposite effect of TXA_2. Prostacyclin, or prostaglandin I2 (PGI2), is a naturally occurring compound produced mainly by endothelial cells in blood vessels. It plays vital roles in the body, including promoting vasodilation (widening of blood vessels), inhibiting platelet aggregation (reducing blood clot risk), and exhibiting anti-inflammatory effects. By regulating blood flow and vascular health,

prostacyclin is significant in cardiovascular function, and its analogs are used in medical treatments for conditions like pulmonary hypertension.[34,35]

Interleukin-1 (IL-1) is a cytokine that plays a pivotal role in the immune response and inflammation, existing primarily in two forms: IL-1α and IL-1β. Produced by various immune cells, including macrophages and monocytes, IL-1 mediates a wide range of physiological processes. It is a key driver of inflammation, promoting the activation and recruitment of immune cells to sites of infection or injury.[36] Additionally, IL-1 can induce fever by acting on the hypothalamus, raising the body's temperature as part of the immune response. It also enhances the activation and proliferation of T-cells, which are critical for adaptive immunity, and plays a role in bone metabolism by influencing bone resorption.[37] Given its central role in inflammatory processes, IL-1 is a target for therapeutic interventions in various diseases, including autoimmune disorders and rheumatoid arthritis. Its activity has been detected in synovial fluids from patients with rheumatoid arthritis. Its actions include activation of lymphocytes and production of fever. Intra-articular injection of highly purified IL-1 cause swelling, accumulation of polymorphonuclear and mononuclear leukocytes, and the loss of proteoglycan from the articular cartilage. The inflammatory changes were like those seen in the joints of rabbits with antigen-induced arthritis.[28,38]

Corticosteroids exert their anti-inflammatory effects by inhibiting the activity of phospholipase A2, an enzyme that plays an important role in the release of arachidonic acid (AA) from cell membrane phospholipids. Arachidonic acid is a key precursor for the synthesis of various pro-inflammatory mediators, including prostaglandins, thromboxane, and leukotrienes, which are involved in the inflammatory response. By blocking phospholipase A2, corticosteroids effectively diminish the availability of arachidonic acid, thereby leading to a significant reduction in the formation of these inflammatory compounds (Figure 7).[28]

The inhibition of phospholipase A2 by corticosteroids occurs indirectly through the upregulation of specific inhibitory proteins, such as lipocortin. These proteins bind to and inhibit phospholipase A2, further curtailing the production of arachidonic acid and its downstream metabolites. This multifaceted mechanism not only minimizes the

inflammatory response but also helps to alleviate associated symptoms, making corticosteroids powerful agents in the treatment of a variety of inflammatory conditions, including asthma, arthritis, and autoimmune disorders. By targeting this critical step in the inflammatory pathway, corticosteroids contribute to a more balanced immune response and promote healing.[28]

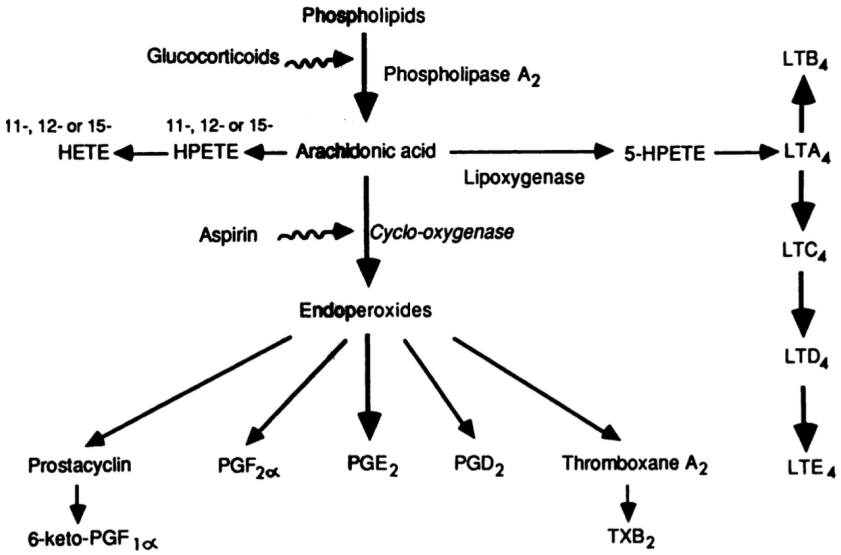


Figure 7. Catabolic pathway of arachidonic acid. Adapted from - Vane J, Botting R. *Inflammation and the mechanism of action of anti-inflammatory drugs*. *FASEB J*. 1(2):89-96.[28]

Corticosteroids, commonly used for their anti-inflammatory properties, exert their effects through a multifaceted mechanism that targets various components of the inflammatory response. As mentioned, one of the primary actions of corticosteroids is the suppression of pro-inflammatory cytokines. By inhibiting the production of these signaling molecules, corticosteroids effectively reduce inflammation and limit the recruitment and activation of immune cells, such as T lymphocytes and macrophages, which are key in perpetuating the inflammatory process. Additionally, corticosteroids stabilize cell membranes, particularly lysosomal membranes, which helps prevent the release of destructive enzymes that can lead to tissue damage during inflammatory responses. Moreover, corticosteroids induce the production of anti-inflammatory proteins like lipocortin, which further inhibit phospholipase A2 and enhance the overall anti-inflammatory effect.[39,40]

At the molecular level, corticosteroids bind to glucocorticoid receptors, leading to the modulation of gene expression involved in inflammation. This interaction promotes the upregulation of anti-inflammatory genes while downregulating pro-inflammatory genes, thereby shifting the balance towards a more anti-inflammatory state.[41] Collectively, these actions of corticosteroids not only mitigate the symptoms of inflammation but also target the underlying biological processes, making them powerful agents in the management of various inflammatory conditions.

1.5 Platelet concentrates

For over two decades, platelet concentrates have been utilized in both medicine and dentistry, primarily aimed at accelerating wound healing. As the understanding of these concentrates has advanced, their capacity to secrete autologous growth factors has been harnessed for a wide range of applications. A substantial body of scientific literature now supports the connection between platelet concentrates and enhanced healing potential.[42,43] This effect is achieved through three primary mechanisms: promoting the revascularization of tissues (angiogenesis), recruiting various cell types, including stem cells, and stimulating the rapid proliferation of diverse cellular populations in the human body (Figure 8). [44]

Numerous platelet products have been developed over the years. These products differ based on several factors related to the techniques used to separate them from whole blood. This is done with various centrifugation protocols and, depending on the protocol involved, the incorporation of anti-coagulant.[44] In the fields of Dentistry and Oral and Maxillofacial Surgery, platelet concentrates were first introduced by Dr. Robert R. Marx and colleagues, beginning in the early 1990s. Their aim was the concentration of blood proteins as a natural source of growth factors (GFs) that would stimulate vascularization and tissue ingrowth based on the fact that blood supply is pivotal for regeneration of all tissues.[45,46,47,48]

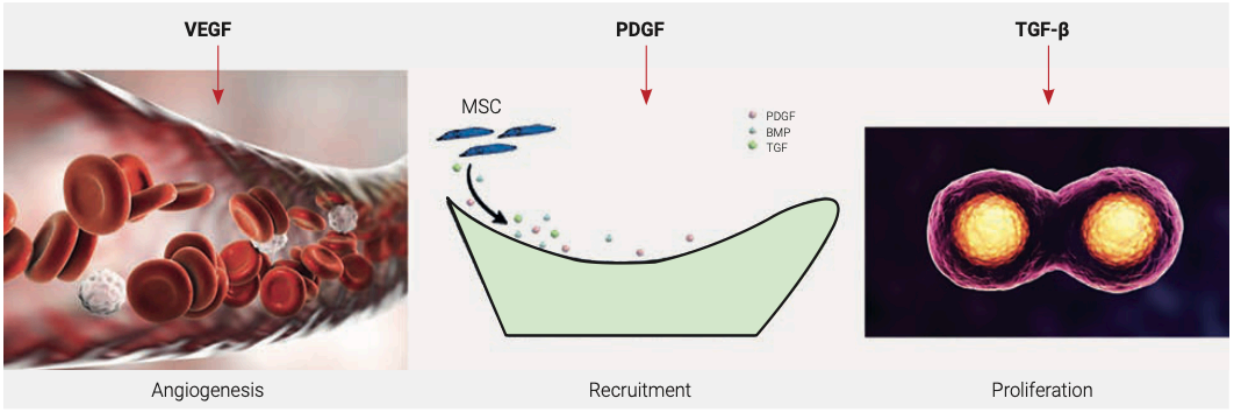


Figure 8. The three main growth factors released from platelet concentrates include VEGF, a known inducer of angiogenesis; PDGF, a known inducer of cell recruitment; and TGF-β, a known stimulator of cell proliferation. Image from Miron RJ, Richard J. *Understanding Platelet-Rich Fibrin*. 1st ed. ProQuest; 2021.[44]

Platelet-rich plasma (PRP), as developed by Marx, is widely regarded as the pioneering form of platelet concentrates. These products were created using intricate centrifugation protocols that included the use of anticoagulants, with the objective of achieving supraphysiologic concentrations of platelets within the plasma layer. The initial protocols typically required 30 minutes to one hour for processing. This foundational concept was further refined at Harvest Technologies at the University of Miami, whose techniques successfully demonstrated the ability to achieve platelet concentrations exceeding 95%.[49,50] Due to the lengthy time required for processing, these initial protocols required anticoagulants in the blood collection tubes. Various anticoagulants have been used, the most popular of which is sodium citrate. Citrate chelates with calcium, preventing the coagulation of blood. These techniques require the reactivation of the coagulation cascade using calcium carbonate or bovine thrombin. Several newer techniques have moved away from anticoagulants, stating that a natural fibrin mesh better concentrates the platelets allowing for more directed growth factor release.[44] Multiple studies, by contemporary leaders in the field, such as Dr. Richard Miron, have demonstrated that removing the anticoagulant from the process increases the ability to form a stable clot, therefore increasing wound healing, such as the body would do in the normal healing process.[51,52]

Other global experts, however, continue to utilize anticoagulants during the processing of blood for the extraction of platelet products. The pioneering group behind the product known as plasma rich in growth factors (PRGF), led by Dr. Eduardo Anitua, advocates for protocols that incorporate anticoagulants in the initial blood collection tubes. These protocols provide clinicians with extended working time and allow for precise control over the initiation of the coagulation cascade. In the absence of such reversal, the product remains in a liquid state, resulting in a rapid release of growth factors rather than a sustained release over several days. This sustained release has been demonstrated to more effectively promote cell growth and tissue regeneration.[53,54]

In the first decade of the 21st century significant changes were made to the centrifugation protocols for platelet concentrates. As mentioned, much of this work was aimed at creating concentrates without the use of anticoagulants. The removal of the use of anticoagulants necessitated much faster spin cycles at a higher centrifugal force ("g-force"). Common centrifugation protocols for these "second generation" platelet concentrates ranged from 2500-3000rpm for 10-12 minutes = ~700g (700 times the earth's gravity). These standardized, reproducible protocols produced a plasma layer composed of a fibrin clot with entrapment of platelets and leucocytes. For this reason, these second-generation products were termed leukocyte platelet-rich fibrin (L-PRF).[44,56,57] The provisional extracellular matrix which forms the L-PRF clot contains leukocytes in addition the numerous growth factors released from the platelets also trapped in the clot (Figure 9). The claimed advantage provided by newer protocols is that they form a stable fibrin clot which demonstrated extended release of growth factors when compared to earlier liquid products.[44] In addition, the incorporation of leukocytes into the final product has been shown to aid in tissue regeneration. Initially it was thought that this was solely based on an increase in host defenses, provided by the leukocytes.[58] This concept is still thought to be of key importance for the use of platelet concentrates for intraoral procedures, such as bone grafting, where leukocytes can participate in phagocytosis of debris, microbes, and necrotic tissue. However, more recent literature has shown that leukocytes can also directly impact tissue regeneration.[59]

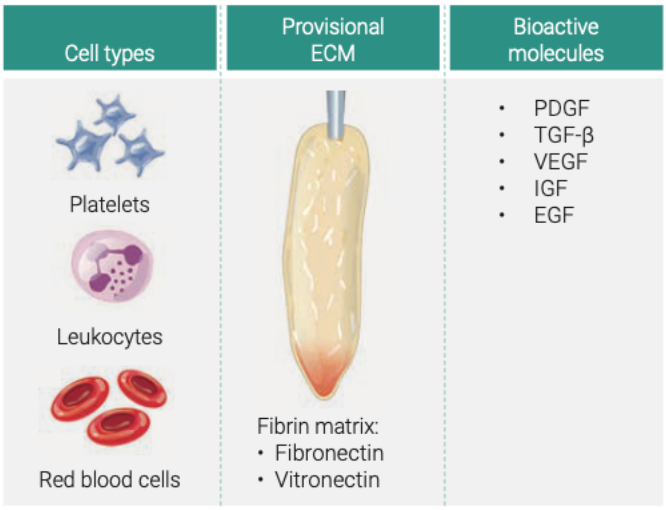


Figure 9. Three main components of PRF all derived naturally from the human body. These include *(1)* cell types (platelets, leukocytes, and red blood cells); *(2)* a provisional ECM 3D scaffold fabricated from autologous fibrin (including fibronectin and vitronectin); and *(3)* a wide array of over 100 bioactive molecules, including most notably PDGF, TGF-β, VEGF, IGF, and EGF. From - Miron RJ, Richard J. *Understanding Platelet-Rich Fibrin*. 1st ed. ProQuest; 2021.[44]

The principle behind platelet concentrates is to enhance tissue regeneration by delivering growth factors in supraphysiologic doses directly to areas of damaged tissue. Normally, the healing process following tissue injury can be categorized into three phases: the inflammatory phase, the proliferative phase, and the remodeling phase. The inflammatory phase commences immediately after injury, characterized by the release of various cytokines and growth factors (GFs) within the first two days. This release initiates a dynamic interaction among endothelial cells, angiogenic cytokines, and the extracellular matrix (ECM), facilitating the accelerated healing of wounds through the organized delivery of these growth factors.[60] Blood plays a crucial role in the healing process by providing essential components that include both cellular and protein products. Concentrating platelets at supraphysiologic doses is made possible by the varying densities of the cell types present in whole blood (Table 3). Due to these differences in density, red blood cells, being the heaviest, settle at the bottom. Above them, white blood cells are found in a distinct layer known as the buffy coat, while platelets, the lightest of the three cell types, accumulate at

the top, mixing with the plasma. This stratification allows for the effective concentration and extraction of platelets and their associated growth factors for therapeutic use.

Table 3. Properties and amounts of cells found in whole blood. Adapted from - Miron RJ, Richard J. *Understanding Platelet-Rich Fibrin*. 1st ed. ProQuest; 2021.[44]

	Platelets	WBCs	RBCs
Density (kg/m3)	1040–1065	1055–1085	1095–1100
Frequency (1/µL)	200,000	5,000	5,000,000
Surface (µm2)	28	330	140
Radius (µm)	11.5	5–7.5	4
Volume (µm3)	14	200	92
Shape	Irregular disc	Spherical	Biconcave

GFs play a vital role in the wound healing process. Their primary functions include facilitating the migration of cells to injury sites, as well as promoting cell adhesion, proliferation, and differentiation. While GFs are present in all tissues, blood serves as the principal reservoir for those involved in tissue regeneration and angiogenesis. The body releases a variety of GFs in a meticulously regulated sequence to initiate complex cellular processes; however, many of these factors have relatively short half-lives. Although recombinant GFs can provide highly concentrated doses of individual factors, platelet concentrates are believed to enhance wound healing by delivering a diverse array of GFs, thereby more closely resembling the body's natural response while still providing supraphysiologic levels.[44,61] The key GFs present in platelet rich concentrates are VEGF, PDGF, TGF-1β, EGF, and IGF.[62]

Vascular endothelial growth factor (VEGF) is secreted by activated thrombocytes and macrophages to damaged sites to promote angiogenesis. The VEGF family is related to PDGF and incudes VEGF-A,-B,-C,-D, and -F. It has previously been isolated and utilized as a recombinant GF. It is considered the most potent growth factor for angiogenesis of tissues, stimulating new blood vessel formation, and facilitating nutrients and increased blood flow

to healing tissue.[63] Additionally, it has strong effects on tissue remodeling, and the incorporation of recombinant human VEGF into various bone biomaterials alone has demonstrated to increase new tissue regeneration.

Platelet derived growth factor (PDGF) acts as a regulator that promotes the migration, proliferation, and survival of mesenchymal cell lineages.[58,64] As the name indicated, platelets are the major source of PDGF, mainly present in platelet α-granules. Of important note PDGF has a very short half-life of around 2 minutes. The ability of newer generation platelet concentrates to form a scaffold and protect PDGF from matrix metalloproteinases has been shown to substantially enhance their prolonged delivery to tissue compared to earlier generation concentrated, such as PRP.[44]

Transforming growth factor beta-1 (TGF-β1) is one of over 30 members of the TGF-β superfamily of growth actors. These factors are predominately thought to mediate tissue repair, immune modulation, and extracellular matrix synthesis.[65] TGF-β1 is the predominant isoform that supports cell proliferation of practically all cell types. Its other actions include angiogenesis, re-epithelialization, and connective tissue regeneration.[61] Platelets are a major source of TGF-β1 production and show specific affinity to bone healing and remodeling.[61]

Epidermal growth factor (EGF) is a critical growth factor for the chemotaxis and angiogenesis of endothelial cells and mitosis of mesenchymal cells. This factor enhances epithelialization and dramatically shortens the overall healing process time when administrated as a recombinant product. EGF is naturally secreted by the body after tissue damage and significantly increases tensile strength of healing tissue. Receptors for EGF are found on most cell types involved in the healing process, including fibroblasts, endothelial cells, and keratinocytes.[66]

Finally, insulin-like growth factor (IGF) is an upregulatory growth factor which increases proliferation and differentiation of multiple cell types.[67] IGF is found in high levels in new generation platelet concentrates because it is released from platelets during their activation and degranulation, which in turn leads to the differentiation of mesenchymal cells. IGF is

also critical in the major axis of programmed cell apoptosis regulation by inducing survival signals, thereby protecting cells from apoptotic stimuli.[67]

Recent observational studies have revealed that platelet concentrates may attenuate postoperative swelling and pain. This has been substantiated by investigations involving human periodontal ligament cells subjected to artificially induced inflammatory conditions. In one such study, human periodontal ligament cells (hPDLC) were cultured with lipopolysaccharide (LPS) to simulate inflammation over a 7-day period, after which liquid-PRF was introduced to the culture medium for an additional 7 days. Immunofluorescence imaging revealed that LPS significantly elevated p65 expression, a key inflammatory marker, which was subsequently diminished by liquid-PRF. Furthermore, other pro-inflammatory markers, including IL-1β and TNF-α, were markedly downregulated, as evidenced by real-time polymerase chain reaction (RT-PCR) analysis.[68] (Figure 10).

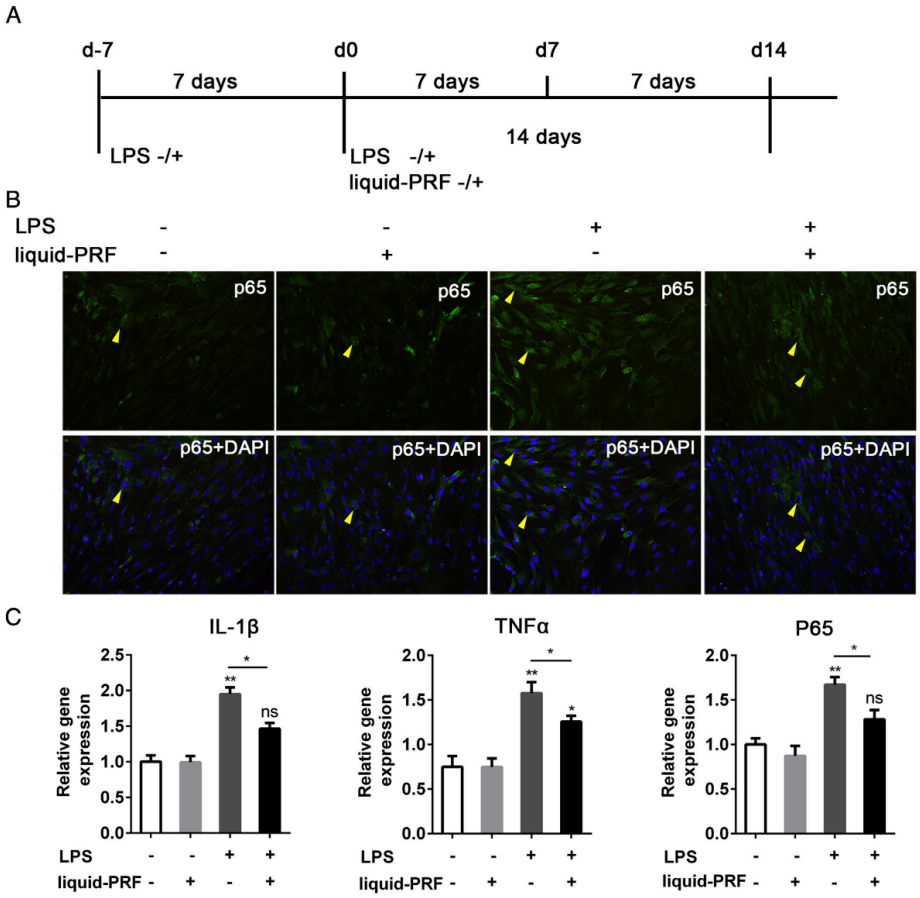


Figure 10. The expression of inflammatory markers in LPS-treated hDPCs. (A) An overview timeline of the experimental setup. (B) Immunofluorescence staining of p65 in hDPCs after cultured with or without LPS and/or liquid PRF. The arrows correspond to areas of enhanced expression of p65. (C) The relative gene expression levels of inflammatory markers including IL-1b, TNF-a, and p65. The error bars correspond to the means 6 standard deviation. Significant differences are indicated: *P , .05, **P , .01; ns, not statistically significant versus the control group. (From - Miron RJ, Richard J. *Understanding Platelet-Rich Fibrin*. 1st ed. ProQuest; 2021.[44]

2 Rationale

Recent literature has examined autologous biologic agents such as plasma rich in growth factors (PRGF) as a treatment of intra-articular pain and dysfunction (IPD). PRGF enhances tissue repair and modulates inflammation. However, the literature remains inconsistent. Some trials report clear clinical gains, whereas others reveal outcomes comparable to placebo or hyaluronic acid. Evidence on PRGF combined with arthrocentesis is scarce and only few randomized controlled trials has explored this protocol. No published data directly compare PRGF to corticosteroid injections after arthrocentesis. Corticosteroids remain the conventional therapy, yet their regenerative effect is limited. Additionally, repeated corticosteroid injections have shown to produce catastrophic degeneration of the TMJ in some patients. The potential of PRGF to promote healing necessitates a direct comparison to establish evidence-based guidance for temporomandibular joint management.

3 Objective

This study aims to determine whether intra-articular PRGF produces better clinical outcomes than corticosteroid injections following standardized TMJ arthrocentesis. The primary outcomes include pain reduction and increase maximum interincisal opening (MIO) across a six-month follow-up. Secondary outcomes include changes in mandibular motion, muscle tenderness and joint sounds.

4 Methods

Ethics were attained for this study through the University of Manitoba Research Ethics and Compliance Department. A Biomedical research ethics board (BREB) full board review certified the final approval for the study in March 2023, followed by yearly reapproval in 2024 and 2025. Ethics #HS25875

4.1 Participants

4.1.1 Inclusion Criteria

Eligible patients were adults aged 18 years or older who had a diagnosis of temporomandibular joint IPD. The diagnosis was supplemented by magnetic resonance imaging (MRI) showing anterior disc displacement with or without reduction. Additional inclusion criteria required the presence of unilateral TMJ involvement with localized pain, willingness to comply with standardized conservative management (including splint therapy, medications and physiotherapy) and appropriateness for arthrocentesis as judged by the treating oral and maxillofacial surgeon.

4.1.2 Exclusion Criteria

Patients were excluded if they were unwilling or unable to comply with conservative therapy, or if arthrocentesis could not be successfully performed (defined as an inability to achieve a 150 mL flush of Ringer's lactate within 10 minutes). Other exclusion criteria included a history of prior TMJ arthrocentesis or arthroscopy, autoimmune or connective tissue diseases, significant mechanical obstruction preventing adequate mouth opening, acute capsulitis, benign or malignant TMJ lesions, neurological disorders, coagulation or blood disorders and known allergies or prior anaphylaxis to study interventions. Pregnant patients and those with severe systemic illness (ASA III or higher) also excluded to ensure safety and homogeneity of the study population.

4.1.3 Randomization and Blinding

A target sample size of 20 patients was planned, with 10 patients per group. Participants were randomized in a 1:1 ratio to receive either a PRGF injection or a corticosteroid (CS) injection immediately following arthrocentesis. Allocation was determined using a simple

randomization sequence. To maintain balance, once 10 patients had been assigned to one treatment arm, all subsequent patients were allocated to the other arm. Due to data collection time restraints, a total of 16 patients ended up being enrolled and successfully treated with arthrocentesis. Eight were allocated to receive CS injection and 8 were to receive PRGF injection.

Blinding procedures were implemented at the patient level. All participants had approximately 10 mL of venous blood drawn during the procedure. In the PRGF group, this blood was centrifuged to prepare approximately 2 mL of PRGF for injection. In the CS group, the blood was discarded. This approach ensured that all patients underwent the same venipuncture and sample handling, thereby preserving patient blinding. The surgeon performing the injection was not blinded due to the visible differences in the injectates.

4.2 Interventions

All participants underwent a standardized unilateral TMJ arthrocentesis performed under intravenous conscious sedation with midazolam, fentanyl and ketamine, combined with local anesthesia. An auriculotemporal nerve block was administered using 1 mL of 2% lidocaine with 1:100,000 epinephrine, followed by 1 mL of 2% lidocaine with 1:100 000 epinephrine administered intra-capsularly. Two standard skin entry points were identified: the first was 10 mm anterior to the tragus and 2 mm below the canthus–tragus line, and the second was 20 mm anterior to the tragus and 5 mm below the same line. An 18-gauge needle was inserted at the first point, and after confirmation of entry into the superior joint space and insufflation of 2 mL of lactated Ringer's solution, a second 18-gauge needle was inserted into the superior joint space at the second point.

The joint was then irrigated under pressure with 150-300 mL of lactated Ringer's solution, with inflow through the first needle and outflow through the second. Following completion of the arthrocentesis and removal of the outflow needle, the assigned injectate was administered. Patients randomized to the CS group received an intra-articular injection of 40 mg triamcinolone acetonide through the inflow needle. Patients randomized to the PRGF group had their autologous blood processed according to standard protocol during the

procedure, yielding approximately 2 mL of PRGF which was injected into the superior joint space in the same manner. All remaining blood products were discarded immediately as biohazardous waste.

After the injection, the inflow needle was withdrawn and the injectate was left in situ. All patients received standardized postoperative care consisting of analgesics (NSAIDs and acetaminophen), nighttime muscle relaxants, a soft diet for one week and four sessions of professional physiotherapy initiated within 1–2 weeks postoperatively. Patients were also instructed in home jaw mobility exercises and stabilization splints were prescribed if clinically indicated.

4.3 PRGF Preparation

PRGF preparation and administration was performed as follows: Once sedation was achieved, a team member trained in venipuncture prepared the patient's arm under sterile conditions. Typically, the right arm is used for IV sedation access, so the left arm was used for blood draw, contingent on vein availability. Venous blood was withdrawn from the participant using standardized 9 mL tubes containing 3.8% sodium citrate as anticoagulant. The blood was centrifuged using the PRGF® System Centrífuge V® at room temperature. The centrifugation protocol was 580g for 8 minutes. The blood was separated into red blood cells at the bottom of the tube and plasma at the top of the tube. The plasma column above the red blood cells was then separated into 2 fractions with a PRGF® Plasma Transfer Device. Fraction 1 (F1) was calculated by subtracting 2 mL from the volume of the plasma column above the buffy coat. Fraction 2 (F2) was the 2 mL of plasma just above the buffy coat. During the collection of F2, attention was be paid not to include leukocytes in the PRGF (the buffy coat). The activation of PRGF was accomplished with PRGF activator (10% calcium chloride) at a ratio of 20 µL of PRGF activator per each 1 mL of F2. The activation was done immediately prior to the intra-articular administration of F2.

4.4 Data Collection

Data collection was performed and recorded on a standardized template (data collection sheet) by an oral and maxillofacial surgery (OMFS) resident-in-training or hospital intern. All team members involved in data collection were trained to provide consistency with data collection. The resident recording the data was not the same resident who was performing the arthrocentesis. Measurements included maximum interincisal opening, lateral and protrusive excursions, muscle tenderness, joint sounds, patients daily average and maximum pain scores on a 10cm visual analog scale (VAS). Joint sounds were recoded along with tenderness to palpation of the muscles of mastication. These same measurements were taken at each follow-up visit (D7, D30, D90, D180) by one of the OMFS residents or hospital interns, using the same data collection sheet.

4.5 Statistical analysis

All analyses were performed using Jamovi software (version 2.6.44) and R Statistical Computing Software (version 4.5.1). Descriptive statistics summarised continuous and ordinal variables as mean ± SD and median (IQR). Categorical variables were reported as counts. Baseline comparability of groups was examined. Between-group differences at each time point were tested using two-sided Mann-Whitney U tests. Change scores were defined as baseline minus follow-up for pain (positive values indicate improvement) and as follow-up minus baseline for MIO (positive indicates improved opening). Within-group changes from baseline to each follow-up time- point were evaluated using the Wilcoxon signed-rank test, while between-group comparisons of change scores (Δ) were assessed using the Mann–Whitney U test. For variables where improvement corresponded to a decrease in score, (pain, tenderness, clicking, crepitus), Δ was calculated as Pre-op − Follow-up, with positive values indicating improvement. Conversely, for variables where improvement indicated an increase in score (range of motion: MIO, excursions, protrusion), Δ was defined as Follow-up − Pre-op, maintaining positive values for improvement.

The primary hypothesis tested the superiority of PRGF over corticosteroid in pain reduction using a one-sided Mann–Whitney U test ($H_0 : \Delta_{PRGF} \geq \Delta_{Steroid}$; $H_1 : \Delta_{PRGF} < \Delta_{Steroid}$),

while all other exploratory outcomes and within-group analyses utilized two-sided tests. Effect sizes for between-group comparisons were calculated using Cliff's delta (δ) to indicate the degree of stochastic dominance, interpreted as small ($|\delta| < 0.33$), medium ($0.33 \leq |\delta| < 0.47$), or large ($|\delta| \geq 0.47$).

Outcome measures

4.6.2 Primary Outcomes

The primary outcomes of the trial were pain reduction, measured using a 10- point visual analogue scale (VAS) for both average daily pain and maximum daily pain and functional improvement, measured by maximum interincisal opening (MIO) in millimeters.

4.6.2 Secondary Outcomes

The secondary outcomes included mandibular movements (right and left lateral excursions and protrusive excursion) measured in mm, muscle tenderness on palpation of the masticatory muscles (scored 0–3 for each muscle and summed per side) and joint sounds. Joint sounds were assessed using an ordinal scale from 0–3:

- **0** – No clicking
- **1** – Clicking audible, only to the patient
- **2** – Clicking audible, to the examiner at close range (adjacent to the joint)
- **3** – Clicking audible, to the examiner from a distance of ≥3 feet

Assessments were conducted at baseline (preoperative), and at postoperative day 7, 30, 90 and 180.

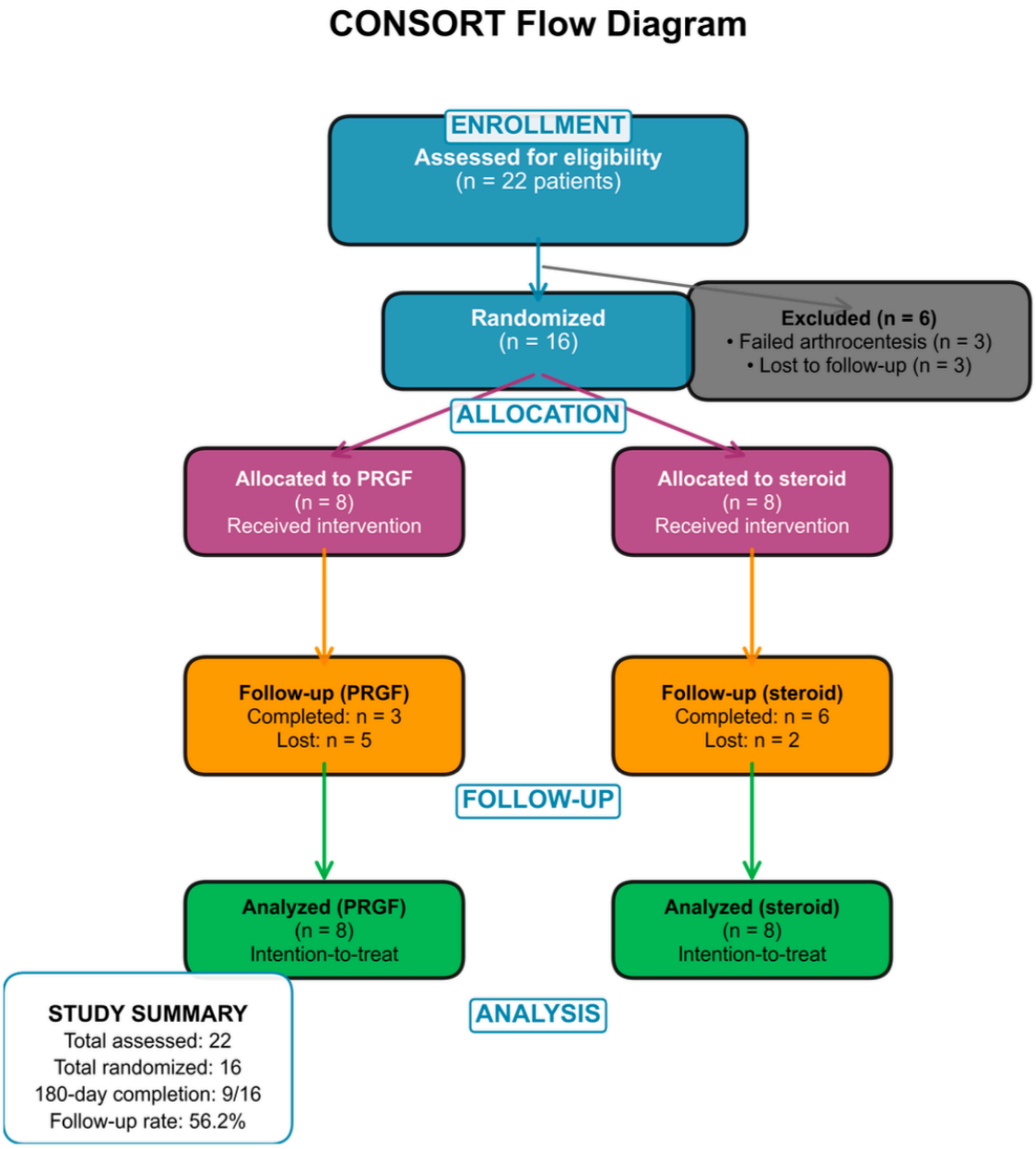


Figure 11. CONSORT flow diagram of patient follow-up.

5 Results

5.1 Participant flow and baseline characteristics

A total of 22 temporomandibular joints (in 22 patients) were enrolled. Figure 11 illustrates the CONSORT flow of participants. Prior to analysis, 6 cases were excluded due to protocol-defined reasons: 3 patients had unsuccessful arthrocentesis procedures ("failed arthrocentesis") and 3 patients were lost to follow-up before the first assessment. This yielded 16 patients with complete baseline data (8 in the PRGF arm and 8 in the Steroid arm) for outcome analysis. Patients were blinded to the injection type, as they were sedated with their eyes covered during injection of the CS or PRGF.

The analysis of final outcomes at Day 180 used a complete-case approach (n = 9 total with data from both Pre-op baseline measurements and Day 180: 3 PRGF, 6 CS), but all available data at earlier time points were used for descriptive longitudinal trends. All participants completed at least one follow-up; five PRGF participants and two steroid participants were prior to day 180.

Baseline demographics are as summarized (Table 4). The PRGF group was slightly younger (median 24 years, IQR 20–55) than the CS group (median 34 years, IQR 31–46). Wilkes classifications were similar between both groups (classes II–III dominating). Baseline pain was higher in the PRGF group (mean 5.63 ± 1.60) compared with the CS group (3.88 ± 2.36) and baseline MIO was larger (mean 41.3 ± 9.0 mm vs 32.4 ± 8.5 mm).

Table 4. Baseline characteristic of participants (median [IQR] or n (%)).

Characteristic	PRGF (n = 8)	Steroid (n = 8)	P-value
Age (years)	24 [20–55]	34 [31–40]	0.40
Sex, female n (%)	8 (100%)	6 (75%)	0.46
Wilkes stage, n (%)			0.28†
• Stage II	6 (75%)	3 (37.5%)	
• Stage III	2 (25%)	4 (50%)	
• Stage IV–V	0	1 (12.5%)	
Joint side (Left/Right)	5/3	4/4	0.59‡
Baseline pain (VAS 0–10)	6.0 [4.75–6.25]	3.5 [2.75–6.0]	0.15
Baseline MIO (mm)	42.5 [38.25–46.0]	29.0 [26.75–39.5]	0.08
Clicking (pre-op) (0–3)	2.0 [1.0–3.0]	1.5 [0.0–2.2]	0.447
Crepitus (pre-op) (0–3)	0.0 [0.0–0.0]	0.5 [0.0–1.0]	0.121
Baseline total muscle pain (0–24)	7.5 [3.25–9.0]	9.0 [3–13]	0.56

5.2 Normality and Test of Choice for our Study Data

All continuous outcomes were tested for normality using the Shapiro–Wilk test. A non-significant Shapiro–Wilk ($p > 0.05$) indicated approximate normal distribution, and a significant result suggested deviation from normality. For normally distributed continuous variables (e.g., Maximum Interincisal Opening and average pain scores), parametric tests were applied: paired t-tests for within-group (pre- vs post-treatment) comparisons and independent-samples t-tests for between-group comparisons. If normality was violated or variables were ordinal, non-parametric alternatives were used. Specifically, we used Wilcoxon signed-rank tests for within-group changes on non-normal or ordinal data and Mann–Whitney U tests for between-group comparisons when the outcome was ordinal (e.g., 0–3 scales for joint sounds and muscle tenderness) or not normally distributed. All tests were two-tailed with $\alpha = 0.05$. For each outcome, results are reported as mean ± standard deviation (SD) or median (interquartile range, IQR) according to distribution. We report 95% confidence intervals (95% CI) for key differences (e.g. changes from baseline and between-group differences) to aid interpretation. Sample sizes (n) per group at each time point are noted, reflecting some loss to follow-up by 6 months. Effect sizes for between-group

comparisons were calculated using Cliff's delta (δ) to indicate the degree of stochastic dominance, interpreted as small ($|\delta| < 0.33$), medium ($0.33 \leq |\delta| < 0.47$), or large ($|\delta| \geq 0.47$).

5.3 Maximum Interincisal Opening (MIO)

5.3.1 Baseline

The two groups had no significant difference in baseline MIO however the PRGF group did start with notably greater opening. (mean ± SD: 41.3 ± 9.0 mm in PRGF vs 32.4 ± 8.5 mm in CS; p = 0.08; Table 1). Baseline MIO values appeared approximately normally distributed in both groups (Shapiro–Wilk p > 0.18), therefore parametric tests were used for MIO.

5.3.2 Within-Group Changes

Neither group showed a statistically significant improvement in MIO from baseline at any follow-up point. In the PRGF group, mean MIO changed by +3.3 mm at D30 and −8.6 mm at D180 (mean decrease, 95% CI: –15.1 to +2.4 mm) but these changes did not reach significance (paired t-test p = 0.65 at 1 month, p = 0.09 at D180). The CS group's mean MIO increased by +5.5 mm at D30 and +7.0 mm at D180 (95% CI: –3.5 to +17.5 mm) but these within-group gains were also not statistically significant (p = 0.11 at D30, p = 0.104 at D180 by paired t-test). Notably, at the D180 final follow-up, the PRGF group had a relatively large decrease in opening (mean 32.7 mm vs 41.3 mm at baseline). The CS group showed a net increase (38.5 mm vs 32.4 mm at baseline).

2.3 Between-Group Comparisons

The CS group exhibited consistent improvement in MIO from baseline, with the largest median increase of 6.5 mm at D180 ($p = 0.104$). In contrast, the PRGF group showed minimal change or slight reduction in MIO across time points (Figure 12). Intergroup analysis revealed significantly greater improvement in the CS group at D180 (Mann-Whitney U = 1.5, Cliff's $\delta = -0.833$, large effect size), with the Hodges-Lehmann estimate indicating a 12.5 mm greater improvement in the steroid group (HL Δ = -12.5, CI: -24.0).

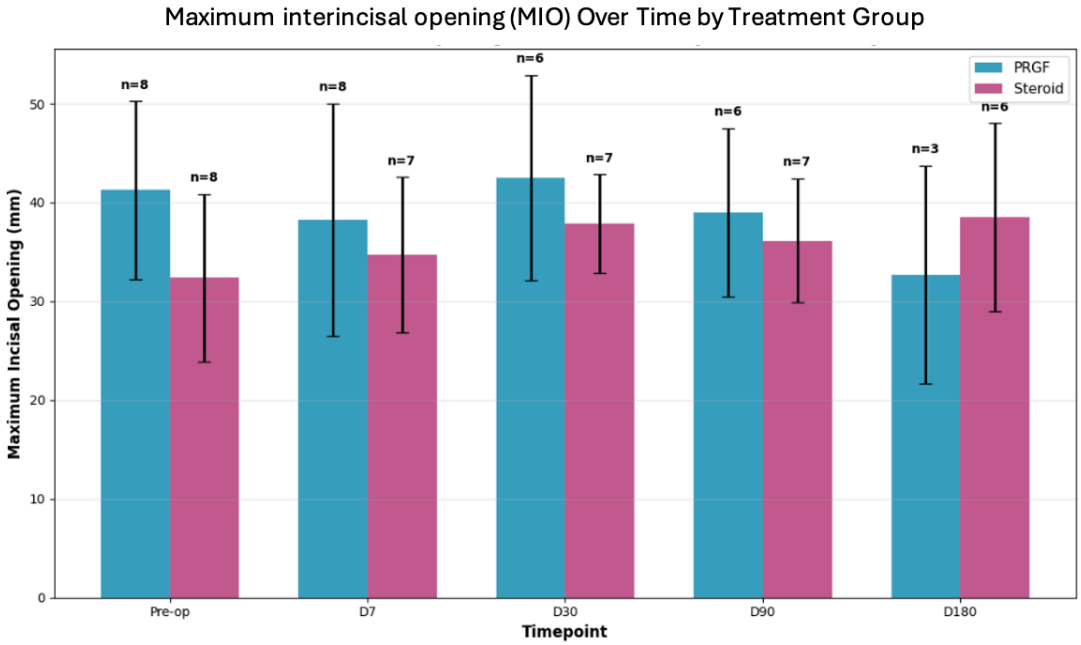


Figure 12. MIO in mm measured at each postoperative timepoint (Pre-op, D7, D30, D90, D180) in PRG and Steroid (CS) groups. Mean ± SD with sample size (n) is displayed above each bar. The Steroid (CS) group showed sustained improvements through D180, while PRGF showed a decrease in MIO.

5.4 Pain Scores

5.4a Average Daily Pain

5.4a.1 Baseline

The PRGF group reported higher average pain at baseline (mean 5.6 ± 1.6 on 0–10 scale) compared to the CS group (3.9 ± 2.4), though this difference was not statistically significant ($p = 0.15$; Table 4). Pain scores were treated as continuous variables and approximately met normality assumptions (Shapiro–Wilk $p > 0.7$ for baseline), as such, parametric tests were used for group comparisons of average pain.

5.4a.2 Within-Group Changes

The PRGF group experienced a significant reduction in mean daily pain from baseline in the early postoperative period. At D30 post-op, average pain in the PRGF group had decreased from 5.6 to 3.8 (mean change –1.5, 95% CI: –2.38 to –0.62), a statistically significant

improvement (p = 0.034, Wilcoxon Signed-Rank Test). This corresponded to a 27% reduction in pain. PRGF pain scores remained lower than baseline at D90 (4.0 ± 2.8, 29% reduction, p = 0.10) but by D180 had risen back near the pre-op level (5.7 ± 2.1, not significantly different from baseline, p = 0.69). In contrast, the CS group's average pain initially improved modestly (from 3.9 to 2.6 at D7 and 2.4 at D30) but these early decreases were not statistically significant (p = 0.11 at D7; p = 0.17 at D30). By D90, the CS group's mean pain (3.6 ± 2.9) had returned approximately to baseline levels (no significant change, p ≈ 1.0 vs baseline). Interestingly, at D180 the CS group's average pain was the lowest recorded (2.3 ± 2.4, about 1.5 points below baseline) but this late improvement was also not significant (p = 0.33) given the variability.

5.4a.3 Between-Group Comparisons

There were no statistically significant differences between the PRGF and CS groups in average pain at any follow-up timepoint (Table 5). For instance, at D30, mean pain scores were 3.8 in PRGF vs 2.4 in Steroid (p = 0.27). By 6 months, the CS group's pain appeared lower on average (2.3 vs 5.7), but variability was high, and the between-group difference did not reach significance (Mann–Whitney p = 0.12). Both treatments were associated with daily average pain reduction over time, especially early after the procedure but the only significant within-group drop occurred in the PRGF group at D30. By the final D180 follow up, the CS group had somewhat better pain outcomes on average (lower pain scores) than the PRGF group, but this difference was not statistically significant.

Table 5: Average Pain Score (0-10 scale) – Mean ± SD (n) for average daily pain in each group and p-values for between-group comparison (independent t-tests at baseline-3 mo; Mann-Whitney U at 6 mo). Negative trends in pain were observed in both groups but no significant group differences.

Time point	PRGF Avg. Pain (Mean ± SD)	Steroid Avg. Pain (Mean ± SD)	p (PRGF vs Steroid)
Baseline	5.6 ± 1.6 $(n = 8)$	3.9 ± 2.4 $(n = 8)$	0.15
1 week	4.3 ± 2.0 $(n = 8)$	2.6 ± 2.2 $(n = 7)$	0.16
1 month	3.8 ± 2.3 $(n = 6)$	2.4 ± 2.1 $(n = 7)$	0.27
3 months	4.0 ± 2.8 $(n = 6)$	3.6 ± 2.9 $(n = 7)$	0.79
6 months	5.7 ± 2.1 $(n = 3)$	2.3 ± 2.4 $(n = 6)$	0.12

5.4b Maximum Pain Intensity

Because maximum daily pain ratings were frequently at the upper limit (many patients reported ”10” out of 10 pre-operatively), these data were non-normally distributed (Shapiro–Wilk $p < 0.01$ at baseline). Therefore, maximum pain data was analyzed with non-parametric tests and summarized as medians. Table 6 presents the median (IQR) of the maximum pain score in each group over time.

5.4b.1 Within-Group Changes

Both treatments produced a significant short-term reduction in maximal pain. In the PRGF group, the median maximum pain fell from 10 (baseline) to 6.5 at D7 and 7.0 at D30 (median decrease of –3 points by D30, $p = 0.03$, Wilcoxon). This improvement persisted at D90 (median max. pain 5.0, $p = 0.04$ vs baseline). However, by D180 the PRGF median max. pain had risen back to 8.0, no longer significantly different from baseline ($p = 0.16$). The CS group showed an even more pronounced early drop in maximal pain: median decreased from 8.5 at baseline to 4.0 at D7 and 3.0 at D30 ($p = 0.03$ at 1 month, Wilcoxon). Unlike PRGF, the CS group’s pain relief was short-lived – by 3 months their median max. pain was back up to 7.0 ($p = 0.89$ vs baseline), effectively reversing the early gains. There was a slight improvement again at D180 (median 5.0), but this remained statistically non-significant compared to baseline ($p = 0.29$).

5.4b.2 Between-Group Comparisons

There were no significant differences between the PRGF and CS groups in maximum pain scores at any time (all Mann–Whitney $p > 0.05$; Table 6). At D7 and D30, the CS group’s maximum pain tended to be lower (median 4–3 vs 6.5–7 in PRGF) but due to variability this did not reach significance ($p = 0.19$ at D7, $p = 0.19$ at D30). By 3 and 6 months, the groups converged (median max pain 5–7, $p \geq 0.77$). Accordingly, PRGF and CS interventions both led to significant reductions in peak pain shortly after treatment; PRGF’s effect persisted a bit longer (through D90) while the CS effect peaked early, regressed by 3 months, but then modestly improved again at D180. At D180, maximum pain levels were lower in the CS group.

Table 6: Maximum Pain (0-10) – Median (IQR) of the maximum daily pain score in each group. P-values from Mann-Whitney U tests compare PRGF vs Steroids at each time (no significant differences).

Time point	PRGF Max Pain (Median [IQR])	Steroid Max Pain (Median [IQR])	p (PRGF vs Steroid)
Baseline	9.5 [8.5, 10.0] ($n = 8$)	8.5 [5.0, 9.0] ($n = 8$)	0.09
1 week	6.5 [5.8, 7.5] ($n = 8$)	4.0 [1.5, 7.0] ($n = 7$)	0.19
1 month	7.0 [3.8, 8.0] ($n = 6$)	3.0 [1.5, 7.0] ($n = 7$)	0.19
3 months	5.0 [3.3, 8.3] ($n = 6$)	7.0 [5.5, 7.5] ($n = 7$)	0.77
6 months	8.0 [6.5, 9.0] ($n = 3$)	5.0 [1.3, 5.8] ($n = 6$)	0.29

5.4.2 Pain Scores Summary

Both treatment groups demonstrated significant reductions in pain intensity over the 6-month follow-up period. As shown in Figure 13, both average and maximum pain scores decreased progressively in both groups, with some return to baseline at D180. Within-group analysis showed statistically significant improvements in maximum pain for both interventions (Table 7). The PRGF group showed significant reductions at D7 (p = 0.017), D30 (p = 0.031), and D90 (p = 0.042), while the CS group demonstrated significant improvements at D7 (p = 0.026) and D30 (p = 0.027).

Despite these within-group improvements, intergroup comparisons proved no statistically significant differences in pain reduction between treatments at any time point (all p > 0.05). However, a trend favouring PRGF was observed for maximum pain at D90 (Cliff's δ = 0.524, large effect size), with the Hodges-Lehmann estimate indicating a 3.0-point greater reduction in the PRGF group.

Table 7. Intragroup Analysis: Significant Wilcoxon Signed-Ranked Test Results

Variable	Time	Group	n	Med (Pre-)	Med(Follow)	Δ	p
Max. Pain	D30	PRGF	6	9.0	7.0	2.0	**0.031**
	D30	Steroid	6	8.0	3.0	2.0	**0.027**
	D7	PRGF	7	9.5	6.5	1.5	**0.017**
	D7	Steroid	6	8.0	4.0	2.0	**0.026**
	D90	PRGF	5	9.5	5.0	3.5	**0.042**
Avg. Pain	D30	PRGF	5	5.5	3.5	2.0	**0.034**
MIO(mm)	D180	Steroid	5	29.0	43.0	6.5	0.104

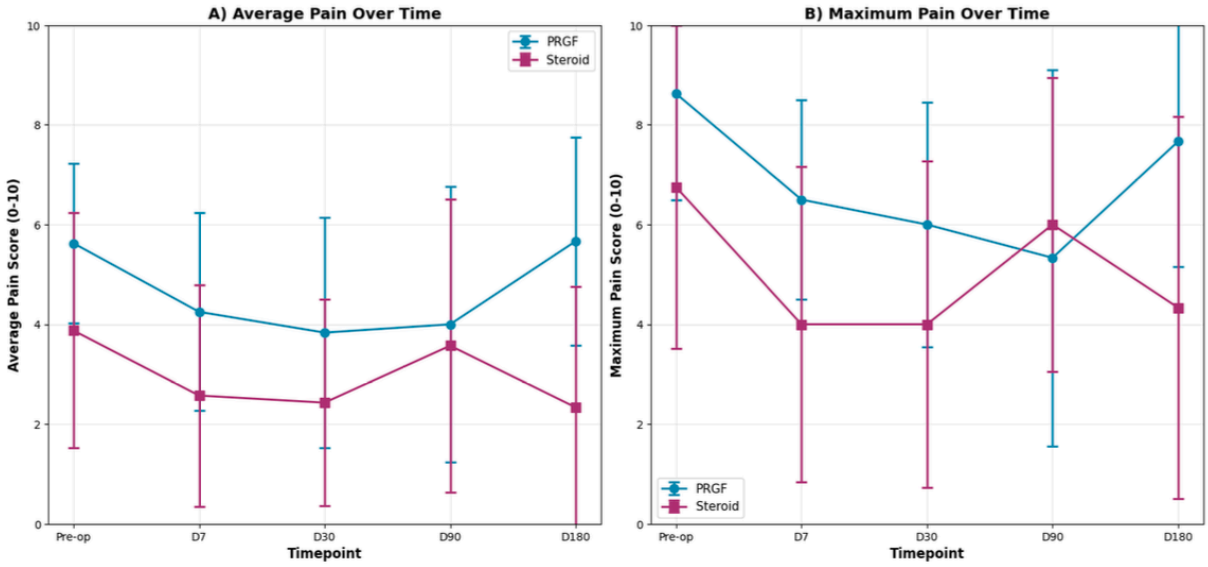


Figure 13. A) Average Pain Over Time and B) Maximum Pain Over Time. Both groups exhibited a reduction in pain intensity over time with no significant between-group difference at any timepoint.

5.5 Joint Sounds: Clicking and Crepitus

Joint sounds were recorded on an ordinal scale (0–3), so non-parametric tests were used for analysis (Wilcoxon for paired changes, Mann–Whitney for group comparisons). Joint sounds were assessed using an ordinal scale from 0–3:

- **0** – No clicking
- **1** – Clicking audible, only to the patient
- **2** – Clicking audible, to the examiner at close range (adjacent to the joint)
- **3** – Clicking audible, to the examiner from a distance of ≥3 feet

At baseline, most patients in both groups had some clicking on the affected joint. There were no significant baseline differences between groups in median clicking or crepitus scores (Table 8).

5.5.1Clicking

Both groups showed a tendency for reduced clicking after treatment, but the changes were not statistically significant. In the PRGF group, median clicking score was 2 at baseline (IQR 1–2.5) and dropped to 1 by D7 and D30, indicating an improvement (fewer clicks); then rose slightly at 3 months and 6 months (median 2.5 at D90, 2.0 at D180). The CS group had a baseline median of 1.5 which improved to 0 (no clicking in most patients) at 1 week, remained low through 3 months (median 0 at D90) and stayed at 0 by 6 months (IQR 0–1.5). Within-group comparisons did not reach significance for clicking (Wilcoxon p = 0.16 in PRGF, p = 0.19 in CS for baseline vs 6 mo). Between groups, there was no significant difference at any time. At 6 months, 4/6 patients in the CS group had no clicking (median 0), compared to 2/3 in PRGF (median 2.0) but this difference was not statistically significant (p = 0.22, Mann–Whitney).

5.5.2 Crepitus

As the study was directed at patients with a low Wilkes score, patients with severe crepitus were not included. Several patients with subjective or inaudible crepitus were included as this did not alter their pre-operative Wilkes score. Crepitus (joint crepitation/grating) was mild in both groups initially (median 0 in PRGF, 0.5 in CS). Following arthrocentesis, crepitus scores remained low. By 6 months, the median crepitus score was 0 in both groups with most patients having no detectable crepitus on exam. There were no significant changes within either group (many patients had zero crepitus both before and after treatment) and no between-group differences at any time (p = 1.00 at D180; Table 8). For example, in the CS cohort, one patient had a crepitus score increase from 0 to 1 (worsening) while two others improved from 1 to 0, canceling out any net change. Overall, both PRGF and CS treatments were associated with stable or slightly reduced joint sounds but the improvements in clicking were not statistically significant and outcomes did not differ appreciably between groups (Figure 14).

Table 8: TMJ Clicking and Crepitus (0-3 ordinal scores) – Median [IQR] in each group. P-values (Mann-Whitney U) indicate no significant group differences at any time point.

Outcome / Time	PRGF Median [IQR]	Steroid Median [IQR]	p (PRGF vs Steroid)
Clicking			
Baseline	2.0 [1.0, 2.5] ($n = 7$)	1.5 [0.0, 2.3] ($n = 8$)	0.63
6 months	2.0 [1.5, 2.5] ($n = 3$)	0.0 [0.0, 1.5] ($n = 6$)	0.22
Crepitus			
Baseline	0.0 [0.0, 0.0] ($n = 8$)	0.5 [0.0, 1.0] ($n = 8$)	0.20†
6 months	0.0 [0.0, 0.5] ($n = 3$)	0.0 [0.0, 0.8] ($n = 6$)	1.00

†Baseline crepitus $p = 0.20$ by Fisher's exact test (both groups had majority zero scores).

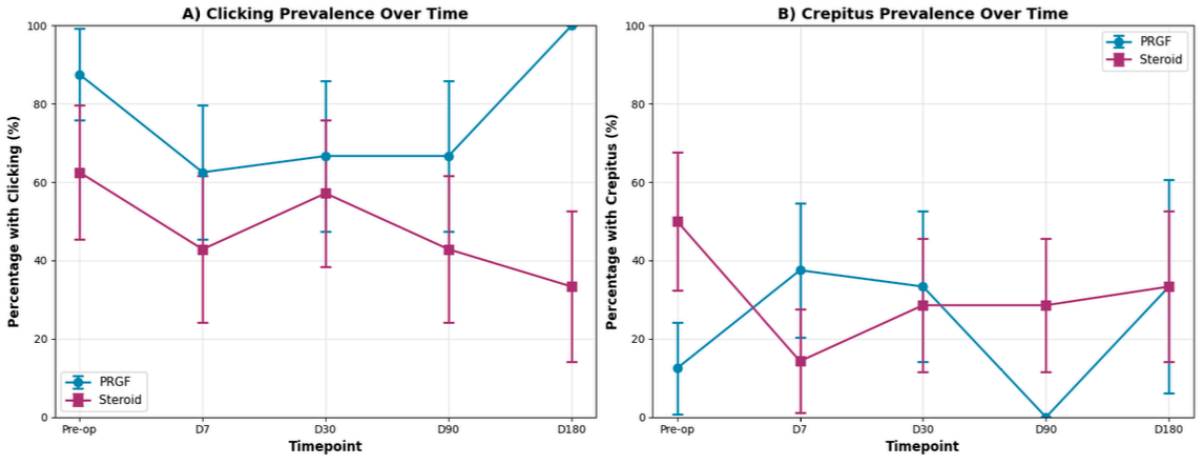


Figure 14. A) Clicking prevalence and B) Crepitus prevalence over time by treatment group. Data are presented as the percentage of patients showing the clinical sign at each timepoint (mean ± SD). Both groups demonstrated a general reduction in joint sounds over the 6 month follow-up periods, with a slightly greater decrease observed in the CS

5.6 Muscle Tenderness to Palpation

Muscle tenderness upon palpation (temporalis, masseter, sternocleidomastoid [SCM], lateral pterygoid; each graded 0–3) was analyzed as change from baseline to the final 6-month follow-up. These ordinal data were evaluated with Wilcoxon signed-rank tests within groups and Mann–Whitney U tests for between-group differences in change scores. Table 9 summarizes the median change in each muscle's tenderness score (negative values indicate an improvement/reduction in pain on palpation).

Both treatments yielded modest reductions in muscle tenderness at some sites but none of the changes were statistically significant ($p > 0.1$ for all within-group comparisons). For

example, in the PRGF group the right masseter tenderness improved by a median of –1 (from median 1 at baseline to 0 at D180) as in the CS group the median change was 0 (baseline and final median both 1; p = 0.23 between groups). The CS group tended to show greater improvements in the cervical muscles: median SCM tenderness decreased by –1 on the treated side and –0.5 on the contralateral side, compared to no change in the PRGF group, but these differences were not statistically significant (e.g. treated-side SCM p = 0.27). The only site where PRGF showed more improvement was the masseter (as noted) and possibly left lateral pterygoid (median change 0 vs 0, essentially no difference). The right temporalis in the PRGF group showed a slight increase in tenderness (+1 median) while it stayed the same in the Steroid group (median 0 change), but again, was not significant (p = 0.17).

Tenderness to palpation decreased slightly in both groups across most muscle groups, reflecting overall clinical improvement in muscle pain over 6 months. However, the magnitude of change was small (generally ≤1 point on a 0–3 scale) and variable and no statistically significant differences were detected between the PRGF and CS groups in terms of reduction in tenderness.

Table 9: Changes in Muscle tenderness from Baseline to 6 Months – Median change in palpation pain score (0-3) for each muscle (negative value denotes improvement). No significant between group-differences were found for any muscle (Mann-Whitney p>0.1)

Muscle	PRGF Δ median [IQR]	Steroid Δ median [IQR]	*p* (between groups)
Right temporalis	+1.0 [+0.5, +1.0]	0.0 [–0.75, 0.0]	0.17
Left temporalis	0.0 [–0.5, +1.0]	–0.5 [–1.75, 0.0]	0.34
Right masseter	–1.0 [–1.5, –0.5]	0.0 [–0.75, +0.75]	0.23
Left masseter	0.0 [–0.5, 0.0]	0.0 [0.0, +0.75]	0.48
Right SCM	0.0 [0.0, 0.0]	–1.0 [–1.0, –0.25]	0.27
Left SCM	0.0 [0.0, +0.5]	–0.5 [–1.75, 0.0]	0.12
Right lateral pterygoid	0.0 [–0.5, +1.5]	0.0 [0.0, +0.75]	0.89
Left lateral pterygoid	0.0 [–0.5, +0.5]	0.0 [0.0, 0.0]	1.00

6 Discussion

The temporomandibular joint is a diarthrodial joint composed of a hinge joint and a gliding joint. The two joint components are separated by the articular disc and its posterior and anterior attachments. The joint is lined with synovium, a metabolically active tissue which secretes synovial fluid containing hyaluronic acid and proteoglycans. This tissue is how the avascular disc obtains its nutrients and oxygenation.[69] It has been shown that the biosynthesis of hyaluronic acid in synovial fluid is inhibited by temporary hypoxia due to increased intra-articular pressure that exceeds the capillary perfusion in overloaded joints, such as that which occurs during parafunctional bruxism.[70] When this process occurs and the lubrication system of the joint fails, increased friction between the joint surfaces and the disc develops, resulting in degenerative changes, including chronic inflammation and subsequent fibrous adhesion and destruction of cartilage (chondromalacia).[71]

TMJ disorder (TMD) is a common musculoskeletal condition of the orofacial region. The disorder is often multifactorial and multifaceted. It can involve the muscles of mastication, the TMJ itself, associated structures such as support ligaments, adjacent nerves, and any combinations of these different aspects. The typical features are pain and restriction of the mandibular range of motion, leading to a decreased quality of life. Intra-articular pain and dysfunction (IPD) is the newly recognized term to diagnose patients with TMD from an intra-articular disease process. The primary goals in the treatment of IPD is to increase the mandibular range of motion and relieve the functional pain of the TMJ.

In many patients, conservative treatment of IPD is highly effective and can preclude the need for surgical intervention.[72] These conservative treatment methods include occlusal splint therapy, physiotherapy, cognitive behaviour therapy, and pharmacologic management with muscle relaxants and anti-inflammatory medication. For patients with persisting symptoms or joint degeneration, minimally invasive treatments may be utilized. These include joint lavage via arthrocentesis or arthroscopy and intra-articular injection of hyaluronic acid, corticosteroids, or other agents on their own or combined with lavage.[24]

Intra-articular injections have been combined with TMJ arthrocentesis and arthroscopy since early in the development of the techniques. Different drugs, such as steroids, opioids, hyaluronic acid, and NSAIDs have been widely studied for this purpose.[73,74,75]. In recent years, platelet concentrates have been added to this repertoire of drugs. Until recent years, most literature on platelet concentrate injections had assessed their benefit when given as monotherapy, not when combined with an arthrocentesis or arthroscopy. Albilia et al investigated the analgesic effects of injectable-PRF (i-PRF) on patients with painful internal derangement. Their research demonstrated that after four rounds of injections, two weeks apart (total 8 weeks of treatment), nearly 70% of patients demonstrated significant reduction in pain.[81]

This report looked to compare the success of two different intra-articular injection agents when combined with office-based arthrocentesis; corticosteroids (CS) and plasma rich in growth factor (PRGF). In this present investigation, neither treatment group demonstrated a statistically significant within-group improvement in MIO at the six-month follow-up. However, the CS group exhibited consistent improvement in MIO from baseline, with the largest median increase of 6.5 mm at the 6-month end point. In contrast, the PRGF group showed minimal change or slight reduction in MIO across time points. Intergroup analysis revealed significantly greater improvement in the steroid group at 6-months, with the Hodges-Lehmann estimate indicating a 12.5 mm improvement in the steroid group. The differences in baseline characteristics, specifically the lower starting MIO and higher Wilkes scores of the CS must be considered when comparing the two groups. This is to say that because the CS group started with smaller MIO, they had more improvement possible. Additionally, Wilkes III patients, with non-reducing discs are expected to have large gains in MIO post-arthrocentesis, whereas Wilkes two patients already have near normal opening prior to treatment.

Several authors have demonstrated findings contradictory to those in our study.[76] Karadayi and Gursoytrak demonstrated that both arthrocentesis alone and arthrocentesis combined with platelet-rich fibrin (PRF) injections resulted in statistically significant improvements in MIO at the three month follow-up, but that the addition of (iPRF) did confer a measurable

advantage over arthrocentesis alone.[77] In another recent study, Chaulagain et al. demonstrated a statistically significant improvement in MIO in patients treated with arthrocentesis combined with injectable PRF (iPRF) compared to arthrocentesis alone, suggesting that adjunctive biologic therapies may offer additional functional benefit under certain conditions.[78] These benefits of PRF were also seen in a study by Ghoneim et al., who reported striking results, with patients undergoing arthrocentesis combined with iPRF achieving an average increase in MIO of nearly 20 mm, a change that markedly surpassed the outcomes of arthrocentesis alone.[79] Again, these findings are in contrast with this present investigation, in which the PRGF-treated cohort exhibited a net reduction in MIO at the six month follow-up.

The second primary outcome assessed was reduction in daily average pain score. The PRGF cohort demonstrated a marked reduction in mean daily pain during the early postoperative period, with average VAS scores declining from 5.6 at baseline to 3.8 at one month postoperatively, representing a 27% reduction. Similar findings have been documented in other investigations, wherein the addition of platelet concentrates to arthrocentesis produced superior analgesic outcomes. One study comparing arthrocentesis alone, iPRF injection alone, and the combination of both found significant pain reduction in all groups at three months, with the combined treatment yielding statistically superior results.[78] Another study, mentioned above, by Ghoneim et al. reported complete pain resolution in all 20 patients treated with arthrocentesis combined with iPRF, a result that significantly outperformed arthrocentesis alone.[79] In the present study, PRGF-treated patients maintained lower intragroup mean pain scores compared to baseline at three and six months; however, these differences did not achieve statistical significance.

The CS group's average pain initially improved modestly then returned to baseline by 3 months. Interestingly, the pain scores then improved again at the 6-month follow-up. The pain reduction in the CS group was notable but not statistically significant.

When comparing between groups there were no statistically significant differences between the PRGF and CS groups in average pain at any follow-up time points. By the final 6 month follow up, the CS group had better pain outcomes on average (lower pain scores) than the

PRGF group, but this difference was not statistically significant, due to high variability within the groups. In their report comparing arthrocentesis alone to arthrocentesis combined with either iPRF or hyaluronic acid, Tepeick showed that pain scores were similar at 1 month between the arthrocentesis alone (AO) group and arthrocentesis combined with iPRF, however, the iPRF group outperformed AO in regard to pain reduction at 3 months.[76] In that study, hyaluronic acid reduced pain more quickly than iPRF in the early phase, but both had similar long-term results. This relates with our findings, where CS provided a slightly better (though not statistically significant) early pain reduction than PRGF, but PRGF showed stronger pain reduction at the one-month follow-up. A key difference is that in Tepeick's study, pain levels in the iPRF group stayed low, while in our study, they returned to baseline after six months. Tepeick's team suggested that platelet concentrates work through regenerative effects, meaning benefits take longer to appear but may last longer. In our report, pain reduction was statistically significant at one month but not at one week, supporting the idea of delayed benefit—however, we did not observe sustained daily pain reduction over time.

The current report also analyzed maximum reported pain. This score represented the maximum pain a patient would experience over the course of the day, in contrast to the average daily pain (which represented the patient's baseline level of discomfort in their TMJ). Few other studies assess maximum pain scores in their results. This data is important, because it provides the patients with improved guidelines on reporting their pain. Often when asked to rate their pain on a VAS, patients want to provide the clinician with two different numbers; one of which is their average daily pain, and another describing how bad the pain can be at its worst. By collecting these data points, it not only allows for additional outcomes to be assessed, but it allows the researchers to be more confident that patients are consistent in their pain score reporting.

In both groups there was a statistically significant short-term reduction in maximum pain. The PRGF demonstrated on-going reduction of maximum pain level at 3 months but a return to near baseline at 6 months. The CS group demonstrated a similar pattern of maximum pain

reduction to that of their average daily pain; the short-term improvements were lost at 3 months but then improved again at 6 months.

When assessing the maximum pain score between groups there were no significant differences noted at any times. The CS group had a lower median pain score at 1 week and 1 month, again perhaps indicating that PRGF takes longer to produce clinically significant pain reduction as suggested by Tepeick.[76] However, these differences did not reach statistical significance. By the 3- and 6-month follow-ups, the median pain scores of the two groups had converged, suggesting that medium differences in intra-articular injection outcomes are minimal with respect to maximum pain scores. It has been postulated that corticosteroids, owing to their anti-inflammatory effects, tend to provide more immediate pain relief, whereas PRGF, through its regenerative properties, may take longer to lead to pain reduction but could potentially yield more sustained benefits. This pattern is partially reflected in our findings, with a more pronounced early reduction in pain observed in the CS group and a significant medium-term improvement noted in the PRGF group. However, by 6 months, the PRGF group had lost its earlier improvement in pain reduction, negating the hypothesized long-term advantage. This data must be interpreted within the limitations of this study.

Joint sounds—including both clicking and crepitus—were recorded as secondary outcome measures in this study. These variables warrant cautious interpretation, as changes in joint sounds do not always accurately reflect the underlying disease state. For example, in a patient with anterior disc dislocation with reduction, a decrease in clicking may occur, not because the joint health has improved, but because disease progression has led to disc displacement without reduction, or even disc perforation, which is typically accompanied by crepitus.

Joint sounds were assessed using an ordinal scale from 0–3. Both treatment groups demonstrated a reduction in clicking following intervention; however, these changes did not reach statistical significance. As mentioned, findings must be contextualized within the known variability of TMJ sound progression. For instance, one patient in this study illustrated the complexity of these measurements: they began with no crepitus (score 0) and loud

clicking audible from ≥3 feet (score 3). Over the course of follow-up, the clicking resolved entirely by six months, yet the patient developed mild crepitus audible only to themselves (score 1). Despite this change in joint sounds, their MIO remained essentially unchanged at 44 mm, and their mean pain score increased slightly from 3 to 4 on a 10-point VAS.

In the PRGF cohort, the median clicking score was 2 at baseline, decreasing to 1 during early follow-up, and subsequently returning to 2 by the final assessment. In the CS group, 4 of 6 patients completing the 6-month follow-up exhibited complete resolution of clicking, including two who initially presented with loud clicks audible from ≥3 feet. One of these four developed crepitus (explained above) while the remaining three finished the study with no joint sounds and an improvement in MIO. In these latter cases, the reduction in joint sounds appeared to correspond with clinical improvement, suggesting that in some—but not all—instances, changes in joint sound profiles may reflect therapeutic benefit.

Muscle tenderness was assessed as part of the current study. These scores were recorded on a subjective pain scale from 0-3 and thus were treated as ordinal data. The muscle pain scores were assessed from the beginning of the study to the end. While muscle tenderness can be related to IPD, it must be distinguished as having a separate pain mechanism. The purpose of including muscle tenderness scores is to two-fold. First, it allows the investigator to see if there is improvement in muscle tenderness following arthrocentesis, and second, it helps rule out any major differences in conservative management techniques directly targeted at myofascial pain.

In the current study both treatments yielded modest but not statistically significant improvements in muscle tenderness at some sites. Palpation tenderness decreased slightly in both groups across all muscle groups reflecting over-all clinical improvement. This may suggest patients in both groups were compliant with consistent post-operative physiotherapy and massage to a similar degree. In their report assessing arthrocentesis alone, PRF alone, or arthrocentesis + PRF, Chaulagin et al. showed a decrease in tenderness of all muscles of mastication which was not statistically significant, and found no significant difference between groups, except for short term improvement in lateral pterygoid pain for the group treated with arthrocentesis and PRF.[78] These results are comparable to our study.

It is critical for the clinician to understand that although there is a relationship between IPD and tenderness of muscles of mastication, intra-articular intervention alone cannot relieve myofascial pain. A complete treatment regimen must be patient-specific, and if myofascial pain is present, adjunctive therapies such as massage, physiotherapy, bruxism appliances, local anesthetic trigger point injections, and Botox injections are warranted.

In summary, the PRGF and CS groups showed comparable outcomes across most measured parameters, with CS showing statistically intergroup benefit in MIO at the 6-month follow-up. Both treatments led to reduced pain over the course of follow-up, with the most notable pain relief occurring in the early postoperative period. PRGF yielded a significant medium-term reduction in average pain (at 1 month) and a sustained reduction in maximum pain through 3 months, while CS provided an early peak pain reduction at 1 week–1 month, and lowest overall pain scores at 6-months. Joint noises (clicking/crepitus) tended to decrease in both groups, especially in the CS group (many patients had resolution of clicking), but variability and small sample size limited statistical significance. Muscle tenderness on palpation improved slightly in both groups without significant between-group differences. Both adjunctive treatments were well tolerated and produced beneficial clinical improvements when combined with TMJ arthrocentesis. No adverse events were noted.

This study has several important limitations. Foremost, the small sample size limited the statistical power to detect significant differences for most outcome measures. Attrition was greater in the PRGF group, further complicating long-term between-group comparisons and reducing the robustness of the follow-up data. The differences in baseline characteristics, although not statistically significant, like did have impact on the changes seen post treatment. Another limitation is the absence of validated quality-of-life assessment tools, such as the Helkimo Clinical Dysfunction Index or the Oral Health-Related Quality of Life instrument for temporomandibular disorder (TMD) patients. These tools have gained increasing acceptance for their ability to standardize the subjective reporting of TMJ-related symptoms and functional limitations, thereby enhancing comparability between

studies.[83,84] An additional limitation which makes comparison of this research to other reports challenging is the vast array of different platelet concentrates available, each with their own proprietary centrifugation technique and unique properties of the concentrate. While this trial utilized plasma rich in growth factor (PRGF), many recent reports have utilized injectable platelet rich fibrin; reporting data on exact centrifugation protocol is lacking in many studies making comparisons additionally complex. No analysis of covariables was performed. The study population was deliberately restricted to patients with Wilkes stage II or III disease to exclude those with more advanced degenerative joint changes, who are less likely to respond to arthrocentesis. While there are isolated reports of success using arthrocentesis combined with platelet-rich fibrin (PRF) in Wilkes stage IV patients, most large-scale investigations support limiting arthrocentesis, whether alone or with adjunctive intra-articular therapy, to cases of disc displacement with or without reduction, rather than more advanced joint pathology. However, due to the regenerative mechanism of platelet concentrates, it is hypothesized that their benefit may be greater for patients with more severe – end stage – joint disease.[27,78]

Future research should aim to recruit substantially larger patient cohorts, incorporate validated quality-of-life instruments, and include an arthrocentesis-alone control group, which was absent in the current study. Additionally, some investigations have directly compared intra-articular injections alone with injections administered in combination with arthrocentesis, while others have explored the potential benefit of repeated intra-articular injections during the follow-up period after arthrocentesis. Given the heterogeneity of TMD patient presentations, it is unlikely that a single, universally optimal treatment approach exists for internal derangement of the TMJ.[27,82] Continued exploration of varied therapeutic combinations, tailored to individual patient profiles, will be essential to refining treatment protocols and optimizing patient outcomes.

7 Conclusion

The present investigation comprised a prospective, blinded, randomized controlled trial involving 16 patients undergoing temporomandibular joint (TMJ) arthrocentesis at the

Health Sciences Centre, Winnipeg, Manitoba. The primary objective was to evaluate whether adjunctive intra-articular administration of plasma rich in growth factors (PRGF) immediately following arthrocentesis yielded superior clinical outcomes compared to intra-articular corticosteroid injections.

The primary outcomes were pain relief and MIO. PRGF failed to outperform steroids on primary or secondary outcomes. Both groups had significant pain reduction from baseline at various points during the study. Pain outcomes were comparable between PRGF and steroids at all post-arthrocentesis time points with the CS group having lowest pain scores at the end of the trial. The CS group showed greater improvement in jaw opening. MIO gains were larger with steroids and a statistically significant difference favouring steroids emerged by the 6-month follow-up (D180). PRGF was inferior to steroids in enhancing maximal mandibular opening at longer-term evaluation. These findings contradict the initial hypothesis of PRGF providing superior clinical benefits over corticosteroid therapy.

The present results contribute to the evolving body of literature on the role of platelet-derived preparations in temporomandibular disorders, indicating that PRGF, when combined with arthrocentesis, does not confer superior benefits compared with corticosteroid injections in terms of pain reduction or enhancement of mandibular mobility. Future research should aim to overcome the current study's limitations, particularly the small sample size and differential attrition rates, by conducting larger-scale randomized trials. Such studies might also incorporate additional comparator groups, including hyaluronic acid and placebo (no adjunctive agent), and should consider incorporating validated quality-of-life and functional outcome measures to capture a more comprehensive assessment of treatment efficacy.

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9 Appendix

Inter-Group Analysis

Table 10. Between Group Analysis

Variable	Time	PRGF Group		Steroid Group		p-value
		N	Median	N	Median	
Average Pain (0–10)	D7	8	4.5	7	3.0	0.937
	D30	6	3.5	7	3.0	0.810
	D90	6	4.5	7	4.0	0.668
	D180	3	5.0	6	2.0	0.966
Maximum Pain (0–10)	D7	8	6.5	7	4.0	0.922
	D30	6	7.0	7	3.0	0.928
	D90	6	5.0	7	7.0	0.387
	D180	3	8.0	6	5.0	0.907
MIO (mm)	D7	8	39.0	7	32.0	0.431
	D30	6	42.0	7	38.0	0.141
	D90	6	41.5	7	37.0	0.125
	D180	3	38.0	6	43.0	0.923
Clicking (0–3)	D7	7	1.0	7	0.0	0.635
	D30	6	1.0	7	1.0	0.500
	D90	6	2.5	7	0.0	0.843
	D180	3	2.0	6	0.0	0.933
Crepitus (0–3)	D7	8	0.0	7	0.0	0.854
	D30	6	0.0	7	0.0	0.604
	D90	6	0.0	7	0.0	0.106
	D180	3	0.0	6	0.0	0.500

Table 12. Between Group Analysis of ROM and Muscle Palpation

Variable	Time	PRGF Group		Steroid Group		p-value
		N	Median	N	Median	
Right Excursion (mm)	D7	8	4.5	7	7.0	0.980
	D30	6	7.5	7	7.0	0.615
	D90	6	7.0	7	7.0	0.743
	D180	3	9.0	6	6.5	0.500
Left Excursion (mm)	D7	8	6.5	7	5.0	0.523
	D30	6	6.5	7	6.0	0.500
	D90	6	7.0	7	8.0	0.787
	D180	3	9.0	6	9.5	0.742
Protrusion (mm)	D7	8	4.5	7	5.0	0.759
	D30	6	5.0	7	7.0	0.827
	D90	6	6.0	7	6.0	0.411
	D180	3	4.0	6	6.5	0.782
Right Temporalis (0–3)	D7	8	0.0	7	1.0	0.198
	D30	6	1.0	7	0.0	0.951
	D90	6	0.5	7	0.0	0.840
	D180	3	1.0	6	0.5	0.942
Left Temporalis (0–3)	D7	8	0.0	7	1.0	0.161
	D30	6	0.0	7	1.0	0.266
	D90	6	0.0	7	0.0	0.569
	D180	3	0.0	6	0.0	0.678
Right Masseter (0–3)	D7	8	0.0	7	0.0	0.710
	D30	6	0.5	7	0.0	0.933
	D90	6	0.0	7	0.0	0.856
	D180	3	0.0	6	1.0	0.167
Left Masseter (0–3)	D7	8	0.0	7	0.0	0.149
	D30	6	0.5	7	0.0	0.689
	D90	6	0.0	7	0.0	0.314
	D180	3	0.0	6	0.0	0.500
Right SCM (0–3)	D7	8	0.0	7	0.0	0.470
	D30	6	0.0	7	0.0	0.637
	D90	6	0.0	7	0.0	0.590
	D180	3	0.0	6	0.0	0.186
Left SCM (0–3)	D7	8	0.0	7	0.0	0.526
	D30	6	0.0	7	0.0	0.348
	D90	6	0.5	7	0.0	0.532
	D180	3	0.0	6	0.0	0.762
Right Pterygoid (0–3)	D7	8	1.5	7	1.0	0.725
	D30	6	2.0	6	1.5	0.829
	D90	6	1.0	7	0.0	0.704
	D180	3	2.0	6	1.5	0.606
Left Pterygoid (0–3)	D7	8	1.0	7	2.0	0.548
	D30	6	1.0	7	2.0	0.500
	D90	6	0.0	7	0.0	0.467
	D180	3	1.0	6	0.5	0.661

Within-Group Analysis

Table 12. Within-Group Analysis of Pain Variable (Pre-op vs Follow-up)

Variable	Time	Group	n	Med (Pre)	Med (Post)	Med Δ	Z	p-value
Avg. Pain	D7	PRGF	8	6.0	4.5	1.0	−1.400	0.926
		Steroid	6	3.0	3.0	2.0	−1.572	0.945
	D30	PRGF	5	5.5	3.5	2.0	−2.023	0.983
		Steroid	5	3.0	3.0	1.0	−1.483	0.935
	D90	PRGF	5	5.5	4.5	1.5	−1.618	0.949
		Steroid	5	3.0	4.0	0.0	0.270	0.393
	D180	PRGF	3	6.0	5.0	1.0	−0.535	0.750
		Steroid	5	3.0	2.0	0.5	−0.944	0.832
Max. Pain	D7	PRGF	7	9.5	6.5	1.5	−2.366	0.991
		Steroid	6	8.0	4.0	2.0	−2.201	0.987
	D30	PRGF	6	9.0	7.0	2.0	−2.201	1.000
		Steroid	6	8.0	3.0	2.0	−2.201	0.986
	D90	PRGF	5	9.5	5.0	3.5	−2.023	0.979
		Steroid	5	8.0	7.0	0.0	−0.135	0.554
	D180	PRGF	2	10.0	8.0	2.0	−1.342	0.921
		Steroid	3	6.5	5.0	0.0	−1.069	0.857

Table 13. Within-Group Analysis of MIO (Pre-op vs. Follow-up)

Variable	Time	Group	n	Med (Pre)	Med (Post)	Med Δ	Z	p-value
MIO (mm)	D7	PRGF	7	42.5	39.0	−2.5	−1.352	0.088
		Steroid	6	28.0	32.0	2.0	1.887	0.971
	D30	PRGF	6	42.5	42.0	0.5	0.105	0.578
		Steroid	7	30.0	38.0	5.0	1.521	0.945
	D90	PRGF	6	41.5	41.5	−1.0	−0.314	0.422
		Steroid	6	30.0	37.0	2.0	1.258	0.897
	D180	PRGF	3	41.0	38.0	−6.0	−1.604	0.125
		Steroid	5	29.0	43.0	6.5	1.618	0.948

Table 14. Within- Group Analysis of Muscle Palpation (Pre-op vs Follow-up)

Variable	Time	Group	n	Med (Pre)	Med (Post)	Med Δ	Z	p-value
Right Temporalis	D7	PRGF	4	0.0	0.0	0.0	0.000	0.500
		Steroid	2	0.0	1.0	0.0	1.500	0.500
	D30	PRGF	5	0.0	1.0	−1.0	1.483	0.064
		Steroid	3	0.0	0.0	0.0	−1.069	0.862
	D90	PRGF	4	0.0	0.5	−0.5	1.095	0.128
		Steroid	2	0.0	0.0	0.0	−1.342	0.910
	D180	PRGF	2	0.0	1.0	−1.0	1.342	0.079
		Steroid	3	0.5	0.5	0.0	−0.802	0.793
Left Temporalis	D7	PRGF	4	0.0	0.0	0.0	0.365	0.353
		Steroid	3	0.0	1.0	0.0	−0.802	0.793
	D30	PRGF	1	0.0	0.0	0.0	1.000	0.159
		Steroid	3	0.0	1.0	0.0	3.000	0.500
	D90	PRGF	2	0.0	0.0	0.0	1.342	0.079
		Steroid	3	0.0	0.0	0.0	−0.802	0.793
	D180	PRGF	2	0.0	0.0	0.0	0.447	0.327
		Steroid	3	1.0	0.0	0.5	−1.604	0.949
Right Masseter	D7	PRGF	6	1.0	0.0	0.5	−0.629	0.741
		Steroid	2	1.0	0.0	0.0	−1.342	0.910
	D30	PRGF	5	1.0	0.5	0.5	−0.944	0.833
		Steroid	4	1.0	0.0	1.0	−1.826	0.971
	D90	PRGF	4	1.0	0.0	0.0	−0.183	0.573
		Steroid	5	1.0	0.0	1.0	−2.023	0.981
	D180	PRGF	2	1.0	0.0	1.0	−1.342	0.910
		Steroid	4	1.0	1.0	0.0	0.000	0.500
Left Masseter	D7	PRGF	3	0.5	0.0	0.0	−1.604	0.949
		Steroid	2	1.0	0.0	0.0	−0.447	0.673
	D30	PRGF	2	0.0	0.5	0.0	0.000	0.500
		Steroid	3	1.0	0.0	0.0	−1.069	0.862
	D90	PRGF	3	0.0	0.0	0.0	−0.535	0.704
		Steroid	3	1.0	0.0	0.0	−0.802	0.793
	D180	PRGF	1	0.0	0.0	0.0	−1.000	0.841
		Steroid	3	0.5	0.0	0.0	0.000	0.500

Table 15. Within-Group Analysis of Muscle palpation – continued

Variable	Time	Group	n	Med (Pre)	Med (Post)	Med Δ	Z	p-value
Right SCM	D7	PRGF	4	0.0	0.0	0.0	−0.365	0.647
		Steroid	2	1.0	0.0	0.0	−1.342	0.910
	D30	PRGF	4	0.0	0.0	0.0	0.183	0.427
		Steroid	3	1.0	0.0	0.0	−1.069	0.862
	D90	PRGF	2	0.0	0.0	0.0	0.000	0.500
		Steroid	3	1.0	0.0	0.0	−1.604	0.949
	D180	PRGF	3	0.0	0.0	0.0	0.000	–
		Steroid	5	1.0	0.0	1.0	−1.348	0.921
Left SCM	D7	PRGF	4	0.0	0.0	0.0	1.095	0.128
		Steroid	3	2.0	0.0	0.0	−1.604	0.949
	D30	PRGF	1	0.0	0.0	0.0	1.000	0.159
		Steroid	1	0.0	0.0	0.0	−1.000	0.841
	D90	PRGF	3	0.0	0.5	−0.5	1.604	0.042
		Steroid	3	0.0	0.0	0.0	−1.069	0.862
	D180	PRGF	1	0.0	0.0	0.0	1.000	0.159
		Steroid	3	1.0	0.0	0.5	−1.604	0.946
Right Pterygoid	D7	PRGF	7	2.0	1.5	−0.5	0.000	0.500
		Steroid	5	2.0	1.0	0.0	−0.270	0.609
	D30	PRGF	3	1.5	2.0	0.0	0.802	0.207
		Steroid	2	0.5	1.5	0.0	0.447	0.327
	D90	PRGF	4	1.5	1.0	0.0	−0.365	0.647
		Steroid	5	1.0	0.0	0.0	−0.674	0.760
	D180	PRGF	2	1.0	2.0	0.0	0.447	0.327
		Steroid	2	1.0	1.5	0.0	1.342	0.079
Left Pterygoid	D7	PRGF	3	2.0	1.0	0.0	−0.802	0.793
		Steroid	3	2.0	2.0	0.0	−0.267	0.607
	D30	PRGF	1	1.0	1.0	0.0	1.000	0.159
		Steroid	3	2.0	2.0	0.0	0.000	0.500
	D90	PRGF	3	1.0	0.0	0.0	0.000	0.500
		Steroid	3	2.0	0.0	0.0	−0.802	0.793
	D180	PRGF	2	2.0	1.0	0.0	0.000	0.500
		Steroid	2	1.0	0.5	0.0	0.000	0.500