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REVIEW ARTICLE

Infiltration of Plasma Rich in Growth Factors for the Treatment of Temporomandibular Joint Disorders: A Comprehensive Review

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Abstract

Temporomandibular joint (TMJ) disorders are a common cause of pain and dysfunction in the orofacial region. In recent years, there has been growing interest in the use of Plasma Rich in Growth Factors (PRFC) as a potential therapeutic option for the management of TMJ disorders. This comprehensive review aims to provide an overview of the biology and current status of PRFC as a therapy for symptomatic internal derangements and inflammatory pathology of the TMJ. The review discusses the potential benefits of PRFC infiltrations in relieving symptoms associated with TMJ disorders, including pain, limitation of mouth opening, and joint dysfunction. The use of PRFC as an adjunctive treatment to splints and as a stimulator of viscosupplementation and regeneration of both joint tissue and subchondral bone tissue is explored. Although the studies reviewed are in intermediate stages and have limited long-term follow-up, they have shown promising results in terms of symptomatology, recovery and treatment stability. However, more research is needed to establish definitive conclusions and determine the optimal delivery protocol for PRFC infiltrations in TMJ disorders. This review serves as a valuable resource for clinicians and researchers interested in the potential use of PRFC as a therapeutic modality for TMJ disorders.

Introduction

The temporomandibular joint (TMJ) is a bilateral ginglymoarthrodial synovial joint located in the craniofacial region. This joint is composed of several key anatomic structures, including the mandibular condyle, mandibular fossa, articular disc, ligaments, and related muscles, which allow rotational and translational movements of the mandible during mastication and other related functions [1].

Temporomandibular disorders (TMD) are a variety of disorders that affect the temporomandibular joint (TMJ) and are characterized by varied symptomatology in the cranial, facial and cervical region [2]. These disorders are considered multifactorial, resulting in symptomatology established by a combination of biological, psychological and social factors [3].

Treatment Perspective

In the initial management of these pathologies it is of vital importance to know the symptoms for which patients consult Maxillofacial Surgery. Among the symptoms we have the decrease of the mouth opening or joint hypomobility, pain in masticatory function, TMJ blockage and clicks or cramps manifested by the patient [4-6].

The direction of the treatment should be focused both on reducing the symptomatology and on controlling the predisposing and perpetuating factors of the pathology, because this is where the failure rates in conservative or non-surgical treatments of the joint are observed. That is why G. Dimitroulis proposes as treatment objectives to reduce or eliminate pain, reduce or eliminate articular noise and restore mandibular function [4-7].

Clinical treatment is successful when worked concomitantly with psychotherapy.

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Table 1: Wilkes classification [7,9].

Stage	Clinical Findings	Radiographic Findings
I	No limitation of opening Painless clicking	Normal disc morphology Mild displacement with early reduction
II	Occasional painful click Intermittent lock	Mild disc deformity Moderate displacement with late reduction
III	Limited opening Frequent painful clicking Joint tenderness	Displaced, nonreducing disc
IV	Limited opening Chronic pain	Severe displacement without reduction Degenerative bony changes
V	Variable joint pain Joint crepitus	Nonreducing disc with perforation Degenerative bony changes

One of the treatment alternatives proposed is the use of growth factors at the same time as the initial surgical or reparative treatment. It is well known that once conservative treatment has not been successful after 6 months, it is necessary to perform the first phase of minimally invasive maneuvers, including arthroscentesis and/or arthroscopy according to the indication based on the Wilkes stages (Table 1) and the level of pain concomitant with the progression of the disease; This is complemented with local pharmacological therapy either infiltrations with corticosteroids, hyaluronic acid (HA) or plasma rich in growth factors in order to perform a viscosupplementation and generate a stable metabolic environment that does not generate degradation of the articular surface [8].

Surgical and Non-Surgical Treatment of Temporomandibular Disorders

Dimitroulis in 2018 published a summary of what could be a treatment guide for the maxillofacial surgeon, it was divided into nonsurgical treatment and surgical treatment [7].

Non-surgical treatment of temporomandibular disorders continues to be the most effective method in 90% of patients. Among the non-surgical therapies are: Psychiatric and neurological management of the patient supported by therapies if necessary, education and self-care by the patient, pharmacotherapy, occlusal therapy, physiotherapy or kinesiology. As for surgical treatments, it is known that only 5 to 10% of all patients require them, ranging from the least invasive (arthroscentesis and arthroscopy) to open techniques (meniscectomy, myotomy, arthroplasty, joint replacement, among others), based mainly on the progression of the disease according to the Wilkes stages mentioned above [7].

Arthroscentesis

The development of arthroscentesis for the temporomandibular joint (TMJ) arose as a consequence of findings observed during arthroscopic lavage and lysis for the treatment of patients with limited mandibular movements. The term was first introduced by Dorrit Nitzan, with her experience and success in managing the superior articular compartment of the TMJ [10].

Arthroscentesis in TMJ is a minimally invasive procedure that allows, by washing the superior articular space, the application of hydraulic pressure to free the articular disc of adhesions, bands of fibrous tissue that form between the articular disc and the capsule, which prevents the free movement of the disc. In addition to eliminating Chemical mediators that accentuate the articular inflammatory processes and its syndromic complex potentiating the articular degenerative processes [10].

Infiltration of Plasma Rich in Growth Factors

Joint infiltration is considered non-surgical conservative therapy when performed concomitantly with occlusal splints, or also when it is adjuvant to lysis and lavage of the joint by arthroscentesis or arthroscopy. It is mainly used for the symptomatic management of internal disorders and/or for acute stages of osteoarthritis. The infiltration improves the level of pain and in turn serves as viscosupplementation of the joint capsule [11].

The objectives of performing infiltration with growth factors in the temporomandibular joint are:

1. Visco or biosupplementation: Term introduced in 1970 and is defined as the restoration of the lubricating properties of the synovial fluid, these being viscosity, shock absorption, elasticity and being responsible for the nutrition of the articular cartilage [11].
2. Generation of a continuous fibrin mesh or matrix on the cartilage surface and in the joint capsule to continuously secrete cell regeneration precursor factors to improve capsule homeostasis, angiogenesis and cartilage regeneration [11].

Growth factors (Table 2) are substances capable of modifying cellular responses, as well as altering

Table 2: Growth factors [12].

Growth Factor	Function
Platelet-derived growth factor (PDGF)	Regulates the secretion and synthesis of collagen
Epidermal growth factor (EGF)	Stimulates cellular proliferation, endothelial chemotaxis and angiogenesis
Vascular endothelial growth factor (VEGF)	Increases angiogenesis and vascular permeability
Transforming growth factor-β (TGF-β)	Stimulates the proliferation of undifferentiated mesenchymal stromal cells (MSCs), stimulates chemotaxis of endothelial cells and angiogenesis
Basic fibroblast growth factor (bFGF)	Promotes the growth and differentiation of chondrocytes and osteoblasts stimulates mitogenesis of mesenchymal cells, chondrocytes and osteoblasts
Connective tissue growth factor (CTGF)	Contributes to joint homeostasis and OA severity by controlling the matrix sequestration and activation of latent TGF-β

in a coordinated manner their proliferation and differentiation, a quality of great importance since by means of platelet concentrates we can guide cellular proliferation of articular cartilage, in order to regenerate the tissue as a consequence of degenerative disorders of the joint, in addition to serving as viscosupplementation and maintaining the homeostasis of the articular capsule, maintaining a balance between the articular surfaces; This translates into a decrease in joint symptomatology and prevents further morphological alteration of the joints [8-12].

As mentioned by Picco, et al., an ideal growth factor in the temporomandibular joint is one that is able to regenerate cartilage regardless of the patient's age and stop the progression of inflammatory joint pathology [8,12,13].

Platelet-rich plasma or plasma rich in growth factors are autologous concentrates well known in the area of implantology and maxillofacial surgery. It is little studied as a drug for the management of internal derangements and/or inflammatory disorders of the Temporomandibular Joint. In 2015 Neukhet published a study conducted in animals, in which joint healing following PRP injection (previously performed bone defects) was comparatively evaluated in each rabbit; [14] Histological analysis of the condyles (condyle with PRP and condyle without PRP) was performed on them; the conclusion was that the infiltrations with autologous blood caused are generation of the articular cartilage as well as a complete healing of the subchondral bone tissue.

It should be emphasized that although the use of growth factors are new for infiltration of the temporomandibular joint, it is necessary to take into account that the infiltration technique may have modifications; this is due to the fact that as it is already known, infiltration is always performed in the upper space of the joint capsule since it is anatomically wider, it is where the inflammatory potential is located and it is the easiest area to access in a blind technique; However, it has been shown that infiltration in the inferior space improves viscosupplementation and mandibular movement, as well as eliminates adhesions between the inelastic zone of the disc in its inferior part [15].

In the literature there is little information showing the technique to access the lower space, since anatomically it is a narrow area and the drug to infiltrate can spread to the infratemporal fossa or retromandibular region; in 2020 Cha and colleagues conducted the first study in which the effectiveness of infiltration was demonstrated in cadavers using the classic blind technique vs. technique guided by ultrasound or ultrasound [16].

It was demonstrated that in the blind technique 80% of the infiltrations were in the superior articular space and 30% in the inferior articular space; while with ultrasound it was 100% in the superior articular space and 90% in the inferior one; this is relevant since the growth factors should be injected in both the superior and inferior compartments; this to take advantage of their regenerative potential and thus stimulate cartilage angiogenesis and differentiation of the mesenchymal cells into chondrocytes, in addition to improving articular lubrication [16].

Discussion

The literature presents heterogeneous studies regarding the effectiveness of growth factors for the management of temporomandibular disorders, initially it must be taken into account that there is a diversity of protocols and funding of these that may actually bias which is more effective.

Although it is clear that there is a real effectiveness in terms of pain reduction and improvement of the function of the infiltrated joints. So far all studies present favorable results in the TMJ; Albilia, et al. showed in 2018 preliminary results about how effective are the growth factors giving favorable results without adverse effects, but the most important thing is that they presented 1-year follow-up and it was shown that these factors continue to act over time so they are characteristics that do not present the corticosteroid or hyaluronic acid [11].

Most studies (80%) show that the use of plasma rich in growth factors (PRGF) was effective and safe as a treatment for joint disorders, whether in the knee, temporomandibular joint, ankle, hip, lumbar facet joint or shoulder, although there are few studies showing the

effectiveness of I-PRF, nor comparison of protocols in the temporomandibular joint.

Wang-Saegusa, et al. in 2011 concluded that intra-articular infiltration of PRGF in patients with knee osteoarthritis has effective and temporary local effects that reduce pain and restore physical function of the joint without causing local or systemic adverse events, thus improving their quality of life. The authors consider PRGF as an effective therapy for the treatment of knee OA [17].

In 2015 Giacomello and collaborators evaluated the effectiveness of PRGF for the treatment of osteoarthritis of the temporomandibular joint demonstrating that patients had a complete or almost complete cessation of pain at the first infiltration and at the second the cessation was complete, so the number of infiltrations is not defined, but it is suggested every 2 weeks according to the evolution of pain in patients [18].

Fernandez, et al. in 2015 when evaluating the efficacy of PRGF application after TMJ arthroscopy in patients with internal derangements Wilkes stage IV, obtained better results in terms of pain reduction and improvement in mouth opening, with respect to the control group, the results were statistically significant only for pain reduction at 6 and 12 months of follow-up, but not at 18 or 24 months after surgery [19].

It is interesting to note that the articles do not conclude which is the best drug to perform infiltration, but it is relevant to highlight that if it is autologous the probabilities of generating side effects are lower, even more in few studies the results are positive for both viscosupplementation and cartilage regeneration. It is here where the importance of the use of ultrasound in infiltrations of the temporomandibular joint must be highlighted, although the study is done in cadavers it was demonstrated that 20% of these infiltrations are erroneous when performed blindly while with ultrasound the efficiency is 100% in the superior articular space; although it is operator dependent the ultrasound technique can generate much more precision in the infiltration of the growth factors and even more if it is performed directly in the inferior space. Generally this type of infiltration is used concomitantly in arthroscentesis and arthroscopy; in the latter the vision is direct, but in arthroscentesis it is a blind technique and the probability of injecting the plasma in the infratemporal, parotidand retromandibular areas is 70% [15,16].

Although the management of temporomandibular disorders is a controversial topic, with a lack of supporting studies to generate an adequate algorithm [20]. However, it has been shown that it is necessary to start from the least invasive to the surgical techniques, so in a study comparing the 3 drugs used in infiltrations (corticoid, hyaluronic acid and PRP) showed that plasma generates a faster and more progressive decrease of pain, with good evolution of the opening and decrease of pain in patients [21].

In filtrations every 2 or 4 weeks with liquid plasma can be used without demonstrated adverse effects and regenerating articular cartilage, increasing bone density in a control time of 1 year; used alone as sole therapy or combined with arthroscentesis and/or arthroscopy, showing better results as coadjuvant therapy [14,22].

Conclusions

- Although studies are not yet sufficient to ensure that growth factors are a better therapy than other drugs for temporomandibular joint infiltrations, it is clear that being an autologous preparation, it has fewer side effects than other drugs and can also last much longer in time compared to hyaluronic acid, generating better intra-articular metabolic conditions.
- Platelet concentrates can serve as a joint biosupplementation therapy following lysis and lavage, as well as a scaffold for articular cartilage regeneration.
- The infiltration technique presents 100% accuracy and effectiveness for the injection of drugs for both the upper and lower space.
- The use of intra-articular platelet concentrates should not be considered as the only therapy for temporomandibular disorders, since, being a heterogeneous pathology, the control of all predisposing factors generates better results.
- Minimally invasive treatments, arthroscentesis and arthroscopy in combination with PRP, corticosteroid and hyaluronic acid show results of improvement of pain, opening and joint noises.

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