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REVIEW ARTICLE

The use of prolotherapy in temporomandibular disorders

O emprego da proloterapia nas disfunções temporomandibulares

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ABSTRACT

BACKGROUND AND OBJECTIVES: The search for minimally invasive treatments for temporomandibular disorders (TMD) has increased in recent years. Prolotherapy, which uses irritant solutions to induce controlled inflammation and tissue regeneration, has emerged as a promising alternative. This article reviews its mechanisms of action, indications, contraindications, application formulas, and clinical outcomes.

CONTENTS: In recent years, research has focused on clinical and minimally invasive treatments for TMD, as well as on determining when and how to apply them effectively. Prolotherapy stands out as a minimally invasive approach that is cost-effective, performed under local anesthesia, replicable, and associated with low morbidity. Its application aims to relieve or eliminate pain and joint dysfunction, making it a promising option in such cases.

CONCLUSION: Prolotherapy, based on the use of dextrose in varying concentrations, has shown encouraging results in the treatment of Temporomandibular Disorders (TMD), particularly in cases of myofascial pain, joint hypermobility, and disc displacement with reduction. By promoting tissue regeneration and stabilizing the temporomandibular joint (TMJ), this technique offers a less invasive alternative with long-lasting results. However, further studies are essential to standardize treatment protocols and to explore its specific indications and contraindications in more detail.

KEYWORDS: Temporomandibular joint, Temporomandibular dysfunction, Prolotherapy.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A busca por tratamentos minimamente invasivos para disfunções temporomandibulares (DTM) tem crescido nos últimos anos. A proloterapia, que utiliza soluções irritantes para induzir inflamação controlada e regeneração tecidual, surge como alternativa promissora. Este artigo analisa sua história, mecanismos de ação, indicações, contraindicações, fórmulas de aplicação e resultados clínicos.

CONTEÚDO: Nos últimos anos, pesquisas têm se concentrado em tratamentos clínicos e minimamente invasivos para as DTM, assim como quando e como empregá-los. A proloterapia destaca-se como uma abordagem minimamente invasiva, de baixo custo, realizada sob anestesia local, replicável e com baixa morbidade. Sua aplicação visa aliviar ou eliminar a dor e a DTM, sendo uma opção promissora nesses casos.

CONCLUSÃO: A proloterapia, baseada no uso de dextrose em diferentes concentrações, apresenta resultados encorajadores no tratamento das disfunções da articulação temporomandibular (DTM), especialmente em casos de dor miofascial, hipermobilidade articular e deslocamento do disco com redução. Ao estimular a regeneração tecidual e estabilizar a articulação temporomandibular (ATM), a técnica oferece uma alternativa menos invasiva com resultados duradouros. Contudo, é fundamental que mais estudos sejam conduzidos para padronizar protocolos, além de explorar de forma mais detalhada as indicações e contraindicações específicas.

DESCRITORES: Articulação temporomandibular, Disfunção temporomandibular, Proloterapia.

HIGHLIGHTS

- Prolotherapy with hypertonic glucose is effective in treating myofascial pain, hypermobility, subluxation, and temporomandibular joint disc displacement with reduction
- Prolotherapy stimulates growth factors, promoting connective tissue repair and reducing or eliminating pain
- Intra-articular injections are minimally invasive procedures that can be used for temporomandibular disorders that are refractory to even more conservative therapies

INTRODUCTION

Temporomandibular disorders (TMD) encompass clinical conditions that affect the temporomandibular joint (TMJ), masticatory muscles and associated structures, causing pain, limited movement and joint noise, it is also one of the main causes of orofacial pain[1-3]. Several treatments have been proposed to manage these conditions, including conservative treatments such as the use of occlusal plates, pharmacotherapy, physiotherapy, minimally invasive approaches such as arthrocentesis and arthroscopy, and more invasive ones such as arthrotomy[4].

In recent years, prolotherapy (PR) has been highlighted in the field of TMD management, especially in cases refractory to conventional treatments. Also known as injection regeneration therapy, it uses irritating substances such as dextrose (PRD) to induce controlled inflammation and stimulate tissue regeneration[5-8]. The present study's objective was to discuss the mechanisms of action, indications, contraindications, dextrose concentrations, application protocol, complications and clinical results in TMD.

CONTENTS

The searches were conducted in the Pubmed, SCOPUS and CINAHL databases for articles published between 1956 and 2024. The following keywords were selected using the National Library of Medicine's MeSH terms in combination: Prolotherapy, Disc displacement with reduction, TMD pain, TMJ disorders, Occlusal splint, Physiotherapy, TMJ injectable agents, Recurrent TMJ dislocation, Hypermobility disorders of TMJ and Myofascial trigger points. In addition, two anatomy textbooks in Portuguese were included in the search, as well as original articles and reviews in English and German that had clinical relevance and practical validity in terms of the possibility of application in the treatment of TMD. Articles that did not involve a practical aspect or that did not present some degree of evidence were excluded. A first selection was made by reviewing the titles and abstracts of all articles found. Next, the full texts of potentially suitable articles were evaluated. According to these criteria, 54 articles were included.

Mechanism of action

PR induces low-grade inflammation through hyperosmolar solutions. Glucose activates GLUT 1-4 channels, promoting the release of water and lipids and triggering temporary inflammation mediated by cytokines[9]. Activation of granulocytes, macrophages, chondrocytes, nerve cells and fibroblasts leads to collagen deposition and contraction, reducing ligament laxity. In addition, the tissue injury caused by the needle stimulates repair through the release of growth factors (platelet, basic fibroblast and insulin-like) and inflammatory mediators (CGRP, bradykinin and prostaglandins)[10]. Administration of hyperosmotic solutions, such as dextrose, activates pain receptors, including those of capsaicin, increasing substance P, CGRP and nitric oxide, which can exert negative regulation on these receptors[11].

Another mechanism involved is tissue glycosylation, which occurs when glucose reacts, not evolving enzymes, with proteins, lipids or nucleic acids, generating advanced glycation end products (AGEs). These AGEs activate receptors such as RAGE, amplifying inflammatory signaling via NF-κB, which stimulates the production of pro-inflammatory cytokines (IL-1β, TNF-α and IL-6). The presence of AGEs also recruits macrophages and immune cells, which release growth factors (TGF-β and VEGF), promoting angiogenesis, tissue regeneration, fibroblast proliferation and extracellular matrix deposition. This process results in fibroplasia and greater ligament stability, which may explain the positive effects of PR on soft tissue repair and reduction of ligament laxity[10].

Indications

PRD has been indicated in some cases of TMD, especially in patients with myofascial pain[12], disc displacement with reduction[13,14], joint hypermobility[15-18] or TMJ subluxation[19].

Contraindications

Although PRD is safe and minimally invasive, there are contraindications, such as systemic or local bacterial infection, use of anticoagulants, needle phobia, musculoskeletal neoplasms, recent progressive neurological deficit, excessive need for sedation, progressive pain unresponsive to anesthetic blocks and allergy to injectable components such as dextrose (corn), sodium morruate (fish) or phenol[20].

Concentration

Several authors have used different concentrations of dextrose in PR to treat joint TMD. Solutions with concentrations of 10%[21], 20%[17], 25%[10], 30%[16] and even 50%[15] have been used. The choice of the dextrose concentration in PR depends on the objective of the treatment, the type of tissue treated and the desired mechanism, whether proliferative or inflammatory. Concentrations below 10% stimulate tissue proliferation without significant inflammation, promoting the deposition of extracellular matrix. Intermediate concentrations (20%-25%) induce controlled inflammation, favoring moderate regeneration. Higher solutions (30%-50%) are used for thick structures, such as joint capsules and ligaments, due to their greater osmotic effect, stimulating the release of inflammatory factors and the healing cascade. High concentrations are indicated for severe ligament laxity or recurrent dislocations of the mandibular head, while lower concentrations are preferable for myofascial pain, minimizing discomfort and adverse effects. However, there is no consensus on the ideal concentration, the choice being based on the clinician's experience and the protocol adopted[10,15-17,21].

Number, volume and sites injected

Studies vary widely as for the number and volume and sites of injections in PR for joint TMD. A single injection site has been used with volumes of 2 mL and 1 mL, respectively, in the superior

posterior ligament of the retrodiscal tissue[10,15]. Three injection sites have been applied, with 2 mL in the superior capsular ligament, located on the lateral margin of the mandibular fossa; in the inferior capsular ligament, close to the mandibular neck; and in the superior compartment of the TMJ[21].

A four-point injection protocol was used: 1 mL in the posterior insertion of the disc with an opening of 10 mm, 1 mL in the superior articular space after maximum opening, and 0.5 mL in the lateral margin of the mandibular fossa and in the mandibular neck at the superior and inferior capsular insertions[17]. Five injection points were used: superior articular space, superior and inferior capsular ligaments, posterior superior disc ligament and stylomandibular ligament (Figure 1), with 1 mL of dextrose solution at each site. The protocol included three monthly sessions, using 2 mL of 30% dextrose, 2 mL of saline solution and 1 mL of 2% articaine or mepivacaine for local anesthesia and patient comfort[16].

Complications

Dextrose, derived from corn, is contraindicated for allergy sufferers. The injection, with a penetration of about one inch, minimizes intravascular risks with prior aspiration. Mild hematomas may occur, especially in light-skinned patients or those with difficulties in anatomical localization[13].

Preparation of the operating field, solution used and injection

With a professional wearing a mask, apron and sterile gloves, the area is antiseptically treated with 0.12% chlorhexidine, sterile drapes are placed and the injection points are marked in the TMJ region with a sterile pen. The injection may or may not be preceded by a regional anesthetic block of the temporal auricle nerve or at the injection site, depending on the technique and solution used[9,10]. PRD infiltration is similar to intra-articular injection in TMJ arthrocentesis. Injections in the face and TMJ must be minimally traumatic due to the rich local innervation, and it is recommended to use a 30G needle and concentrations of 10% to 50% dextrose, depending on the professional's experience. If the option is 12.5% dextrose, the solution should be prepared in a 3 mL syringe, using a 25G needle to aspirate 0.75 mL of 50% dextrose, 0.75 mL of distilled water and 1.5 mL of 2% lidocaine. The air must then be removed and the needle used for aspiration must be replaced with a 30G[22-25] needle before the procedure is carried out.

It begins in the posterior articular space. The lateral pole of the mandibular head is palpated while the patient opens and closes their mouth, identifying the depression anterior to the tragus. The point is marked and the needle is inserted at 2.5 cm, directed anteromedially towards the medial wall of the mandibular fossa. After aspiration to avoid vessels, 1 mL of the solution is injected. Next, the injection is made into the anterior portion of the disc and the upper head of the lateral pterygoid muscle. To locate this area, the physician should observe the slight depression anterior to the mandibular head with the mouth closed and mark this point before the first injection, as palpation can be difficult.

The needle is inserted into the marked point, angled anteromedially, at the same depth, followed by aspiration and injection of 1 mL of the solution. The third point corresponds to a myofascial trigger point (MTP) at the origin of the masseter muscle near the zygomatic arch. So that it is easier to locate, the patient is asked to clench their teeth, outlining the muscle. The most sensitive point is marked. The patient then relaxes their jaw and 1 mL of the solution is injected directly into the area, using the same depth as the needle. The objective of this protocol is to guarantee precision in the application, optimizing the therapeutic effects and minimizing discomfort for the patient[13]. Once the injections are complete, the areas marked with the pen are removed. This procedure is carried out three times, at fortnightly or monthly intervals, depending on how the case progress[4,13,16]. It is recommended that the patient returns for evaluations after 30, 90 and 180 days[15,26].

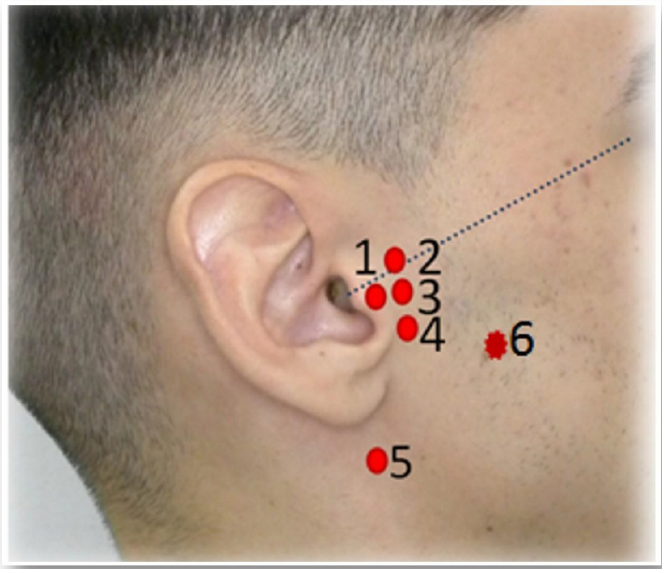

Figure 1. Injection points. Adapted[16]. 1. posterior insertion of the disc; 2. superior capsular insertion; 3. superior articular space; 4. inferior capsular insertion; 5. stylomandibular ligament; 6. origin of the masseter muscle.

CLINICAL RESULTS

The effectiveness of PRD in the treatment of TMD will be analyzed below, with specifications for each relevant condition.

Myofascial pain

One study included 64 patients with myofascial pain, who were divided into three groups for injections in the MTP: 5% aqueous dextrose (Group DA, n=23), saline solution (Group SS, n=20) and 0.5% lidocaine (Group L, n=21). Pain was evaluated using the Visual Analog Scale (VAS) and the pressure threshold using an algometer, before, immediately after and seven days after the injections. The mean pain intensity was 6.78 before,

5.19 immediately after and 3.39 after seven days, with a greater effect after the second and third injections. The pressure threshold increased by 0.37 immediately after and by 0.42 after seven days. After one week, only the DA Group had a significant reduction in the VAS score (2.39 vs. 3.85 in the SS and 4.05 in the L, $p<0.01$) and a significant increase in the pressure threshold (2.49 vs. 1.91 in the SS and 2.07 in the L, $p<0.05$). The authors concluded that 5% dextrose is the best option for injection in the MTP[12].

Disc displacement with reduction

A study compared the effectiveness of two different treatments: PRD12.5% and deep dry needling therapy (DDNT) in a sample of 40 patients with anterior disc displacement with reduction (ADDR). This randomized clinical trial evaluated the impact of each therapy on pain relief, functional improvement and patient symptoms. The results indicated that both treatments were effective in improving symptoms related to ADDR. However, PRD showed superior effects in terms of pain relief, improved jaw function and symptom reduction compared to DDNT. This suggests that PRD may be a more effective option for treating this condition, offering more significant clinical benefits[14].

Subluxation

A randomized clinical trial compared botulinum toxin A (TxB-A) and PRD in 30 adults with TMJ subluxation, 25 of whom completed the study. The TxB-A group (n=11, mean age 25.64 years) received 40U in the lateral pterygoid muscles, while the PRD group (n=14, mean age 32.37 years) received three sessions of injections around the TMJ. The frequency of locking was assessed at the beginning and after 8-12 months, and patient satisfaction only at the end. Both groups showed a significant reduction in locking episodes ($p<.01$), with no difference between them ($p>.05$). Seven patients in the TxB-A group (63.6%) and eight in the PRD group (57.1%) did not report locking episodes, with similar satisfaction in both groups ($p>.05$). The findings indicate that PRD and TxB-A are equally effective in reducing locking and patient satisfaction[19].

Another randomized clinical trial[17] evaluated different concentrations of PRD at 10%, 20% and 30% versus saline as a placebo in the treatment of TMJ hypermobility in 40 patients with mandibular subluxation or dislocation. All received injections in four areas of the TMJ for four months. After treatment, all groups showed an improvement in pain, a reduction in mouth opening and joint sounds, with no episodes of locking. There were no statistical differences between the groups, indicating that no concentration of dextrose was superior to the placebo.

Joint hypermobility

A randomized clinical trial evaluated PRD compared to placebo in the treatment of TMJ hypermobility. Of the 30 patients recruited, 26 completed the study, 12 in the placebo group and 14 in the PRD group. The placebo group received saline injections, while the PRD group received 30% dextrose, both administered in five ligament and joint areas. Pain was assessed by the VAS, and maximum interincisal opening (MIO) was measured preoperatively and after 12 months. Both groups showed improvement in pain and joint sounds, with an increase in masticatory efficiency. However, MIO was significantly reduced only in the PRD group. There were no statistically significant differences between the groups in the primary outcome variables, suggesting that PRD was not superior to placebo in the treatment of TMJ hypermobility[16].

DISCUSSION

Joint diseases such as disc dislocations, hypermobility, subluxation and dislocation of the TMJ should always be treated conservatively first. Various therapies are indicated, such as the use of occlusal devices and manual therapy, low-intensity photobiomodulation and isolated arthrocentesis[27-32]. When these therapies fail, an interesting option may be the use of PRD[12-19,21]. PRD involves intra- and periarticular injections to strengthen the TMJ capsule and ligaments, promoting fibroblast proliferation and relief of pain. In cases of subluxation and disc displacement, it offers advantages such as: being less invasive, being performed in an outpatient setting, low cost, rapid execution and lower risk of morbidity, such as facial nerve damage. However, it requires multiple applications and there is still little data on its long-term effects, especially on articular cartilage[27].

The concentration of dextrose can determine whether it will have an inflammatory characteristic or not. Some authors mention that when the concentration of dextrose is below 10%, it directly promotes cell and tissue proliferation without causing inflammatory reactions[15,21]. On the other hand, when the concentration is higher than 10%, it generates local tissue trauma due to its osmotic effect, which triggers inflammatory reactions, stimulating healing and tissue repair. One possible mechanism attributed to glucose is its ability to increase the proliferation of osteoblasts and chondroblasts from synovial tissue progenitor cells, which could contribute to the repair of TMJ intra-articular structures[33-40].

It is possible that there is an association between the injection site and a positive outcome[15,41-44]. It is recommended that in cases of joint hypermobility, intracapsular injection should be used[45-48]. However, when there is pain, joint hypomobility, disc displacement and joint sounds, the best options are injection into the retrodiscal tissue and into the superior or inferior compartments of the TMJ. When joint hypomobility is present, especially if it is related to adhesions or early-stage adhesions, injecting dextrose will only increase this joint condition, due to the increase in local fibroplasia. In this case, the indication is for arthrocentesis or other surgical treatments[32,49,50-52]. If the option is to inject dextrose into the lower compartment, when disc displacement and joint sounds are present, it should be done with ultrasound guidance[53]. In the case of pathological changes in this joint, there may be adhesions between the upper pole of the mandibular head and the lower portion of the disc, which further reduces the volume of the lower compartment, making the needle penetration and injection more difficult.

PRD is a viable, effective, low-cost and safe option. It is well accepted by patients and has no significant adverse effects[21]. When comparing PRD with TMJ arthrocentesis, the two are similar in that they use needle injections, however, PRD mainly injects dextrose in varying concentrations[54] alone[17] or combined with anesthetics[55] and saline solution[16] into the connective tissue around the TMJ[18], while arthrocentesis injects saline solution into the joint space, combined or not with hyaluronic acid, platelet-rich fibrins, PRP[56,57]. In patients with intra-articular TMJ alterations that don't respond to conservative methods, PRD can be a viable alternative before the indication of more invasive surgical treatments[18,58,59].

Some authors indicate that no concentration of dextrose is superior in TMJ PR, all being effective in improving hypermobility symptoms. However, PR with 10% dextrose may be sufficient to treat this condition[17]. PR can reduce the need for drugs in TMD patients, improving quality of life.

Studies show that PRD has an analgesic and functional effect, reducing the use of analgesics and anti-inflammatory drugs. Its mechanism is based on inducing controlled inflammation, promoting tissue repair and ligament strengthening, reducing hypermobility and pain. In addition, by minimizing the adverse effects of non-steroidal anti-inflammatory drugs, such as gastrointestinal and cardiovascular complications, PRD is a safe, minimally invasive and long-lasting option[17,21]. Nevertheless, it's important that each case is assessed individually to ensure the appropriate indication.

One of the main challenges of PR is the need for multiple injection cycles to achieve satisfactory results, which prolongs treatment and requires greater patient commitment. Accuracy can be affected by anatomical variations and the absence of ultrasound, but proper training and the use of imaging techniques minimize these limitations, making PRD a viable option for TMD[17,60-62]. Faced with the challenges of PR in TMD, it is recommended to start with an injection at a single strategic point, such as the posterior superior ligament of the retrodiscal tissue, to assess the therapeutic response and minimize the invasive aspect of the treatment. If necessary, infiltration can be extended to other anatomical points[10]. Further research is essential to standardize protocols, including the minimum effective dose, the ideal interval between applications and the number of cycles required. This will make it possible to individualize treatment, optimize results and consolidate PR as an evidence-based option in the management of TMD.

CONCLUSION

PRD was effective in managing TMD, especially myofascial pain, hypermobility, subluxation and disc displacement with reduction. It is a minimally invasive alternative which promotes tissue regeneration and TMJ stabilization with good results. Nevertheless, further studies are needed to standardize protocols and better define indication. Careful patient selection and evaluation of contraindications are essential to optimize results and reduce risks.

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AUTHORS' CONTRIBUTIONS

Eduardo Grossmann: Data Collection, Conceptualization, Methodology, Writing - Preparation of the original, Writing - Review and Editing, Supervision and Visualization.
Rodrigo Lorenzi Poluha: Conceptualization, Writing - Preparation of the original, Writing - Review and Editing, Supervision and Visualization.