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Clinical Evaluation of Prolotherapy in Management of Temporomandibular Joint Hypermobility

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Abstract:
Aim*: To evaluate the efficacy of using prolotherapy in management of temporomandibular joint hypermobility.*
Patients and Methods: *A prospective, randomized, double-blind clinical study using a placebo control was carried out. Thirty patients with painful subluxation or dislocation of the TMJ were randomly assigned to 1 of 2 equal-sized groups. Patients in the active group received 3 injections of dextrose (2 mL of 10% dextrose and 1 mL of 2% mepivacaine) for each TMJ, each 4 weeks apart, whereas patients in the placebo group received injections of placebo solution (2 mL of saline solution and 1 mL of 2% mepivacaine) on the same schedule. A verbal scale expressing TMJ pain on palpation, maximal mouth opening (MMO), and frequency of luxations (number of locking episodes per week) were assessed at each injection appointment just before the injection procedure and one months,and one year after the last injection. The collected data were then statistically analyzed.*
Results: *By the end of the study, each group showed significant improvement in TMJ pain on palpation and number of locking episodes and significant improvement in MMO.*
Conclusion: *Prolotherapy with 10% dextrose appears promising for the treatment of symptomatic TMJ hypermobility, as evidenced by the therapeutic benefits, simplicity, safety, patients' acceptance of the injection technique, and lack of significant side effects. However, continued research into prolotherapy's effectiveness in patient populations with large sample sizes and long-term follow-up is needed.*
Keywords: *TMJ hypermobility – CBCT – Prolotherapy – Dextrose*

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I. Introduction:

Hypermobility disorders of the temporomandibular joint (TMJ) can be defined as hypertranslation of the mandibular condyle anterior and superior to the articular eminence during mouth opening **(1)**. Although no definite classification scheme exists yet it can be commonly classified as: subluxation, acute, chronic and recurrent dislocations (luxation) of the TMJ **(2)**. Subluxation is defined as a self-reducing partial dislocation of the TMJ, during which the condyle passes anterior to the articular eminence **(3).**

Honda *et al*.**(4)**determined that CBCT has diagnostic capabilities equal to or greater than those of helical CT. CBCT has high-diagnostic accuracy in the assessment of osseous TMJ structures.**(5)**. The treatment of chronic symptomatic TMJ hypermobility may be organized into; bony alteration, alteration of associated musculature and alteration of the ligaments.**(6)**.Ligament alteration involves various therapeutic approaches have been designed to limit the forward excursion of the condylar head mainly by tightening and limiting capsular laxity. These approaches involve capsular plication, ligamentorrhaphy, immobilization of the mandible and prolotherapy (sclerotherapy). Proliferative injection therapy (prolotherapy), also known as "regenerative injection therapy" and "growth factor stimulation injection," has been used to improve human ligament, tendon, and joint healing for more than 60 years. .Prolotherapy injections proliferate or stimulate the growth of new, normal ligament and tendon tissue. **(7)** In human studies on prolotherapy, biopsies performed after the completion of treatment showed statistically significant increases in collagen fiber and ligament diameter of up to 60%.**(8)** Various agents have been used for prolotherapy including psyllium seed oil,**(9)** dextrose**(10)**and combinations of dextrose, glycerine and phenol.**(11)** However, hypertonic dextrose is commonly used, as it is inexpensive, readily available and reported to be safe.**(12,13)**.

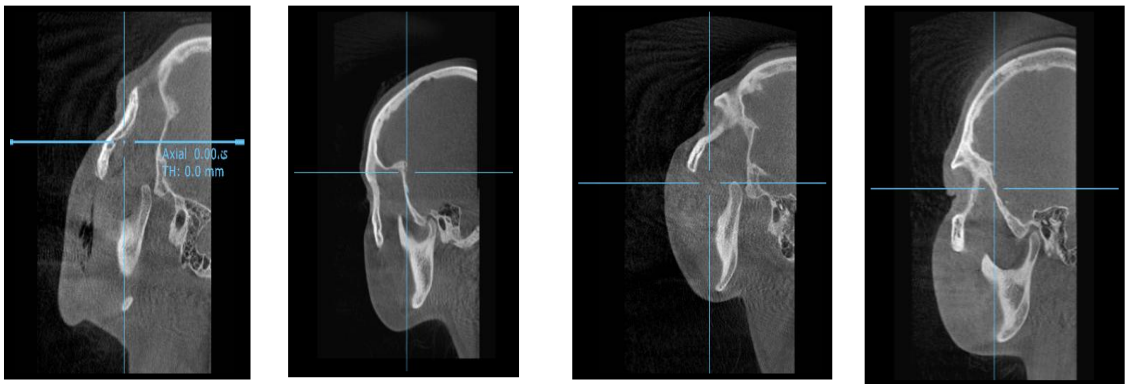
While a number of trials have been conducted on the effects of dextrose prolotherapy on TMJ hypermobility, inflammation initiates the biological process of wound healing. following injury, granulocytes migrate into the injured tissue, monocytes and macrophages follow the granulocytes to the wound site. Growth factor is released and activates fibroblasts, which produce matrix and new collagen fibrils. Unfortunately, the healing process is often incomplete as the new collagen fibrils grow at right angles to the plane of the injury and do not necessarily aligne with the original connective tissue.[(14)] Histologic studies demonstrate fibroblast proliferation originating in the periosteum following injection of prolotherapy solution. Periosteal blood flow facilitates the repair which is critical considering the relative avascularity of tendons and ligaments.[(15)]. Dextrose can cause cell growth by other mechanisms. Research in diabetics has shown that direct exposure to dextrose can cause certain types of cells to grow, and cells in an environment with an osmotic gradient shrink and produce an increase in growth factors.[(16)]. Prolotherapy has been used successfully in many joints in the body and can be used for nearly any tendon or ligament problem in the head or neck. The fact that much of the pain of TMD originates outside the TMJ suggests the usefulness of prolotherapy in treating extracapsular tendon and ligament disorders.[(17)]

II. Patients And Methods:

Study Design Patients:

The present study was double blinded randomized clinical study conducted in faculty of Dentistry, Suez Canal University after the approvalof the Research Ethics Committee, REC (4/2017)

Thirty patients suffering from TMJ symptomatic hypermobility were included in this study. They were interviewed and clinicaly examined at the outpatient clinic of the Oral and Maxillofacial Surgery Department, Faculty of Dentistry, Suez Canal University. The criteria of inclusion in this study were criteria for inclusion in this study were the presence of a diagnosis of painful subluxation or dislocation of the TMJ in the absence of medical conditions that may significantly interfere with healing and willingness to follow instructions. The radiographic observation by CBCT of anterior positioning of the mandibular condyle to the articular eminence on wide opening confirmed the clinical diagnosis(Fig 1). The study program was explained to the patients, who gave informed consent to undergo treatment. After agreeing to be enrolled in this study, each patient was randomly assigned to 1 of 2 equal-sized groups. Patients in the active group received 3 injections of dextrose solution (2 mL of 10% dextrose and 1 mL of 2% mepivacaine), each 4 weeks apart, whereas patients in the placebo group received injections of placebo solution (2 mL of saline solution and 1 mL of 2% mepivacaine) on the same schedule. We used 3-mL injection syringes with 30-gauge needles. The dextrose solution (2 mL of 10% dextrose and 1 mL of 2% mepivacaine) and the placebo solution (2 mL of saline solution and 1 mL of 2% mepivacaine) were prepared by the same colleague so that the loaded syringes resembled each other in size and color. Local anesthetic was included in the injected solution for post-injection comfort. The solutions were identical in color. Only that colleague had access to the treatment codes, and we were not aware of the randomization codes until the study was completed.



A **B** **C** **D**

Fig. (1) : (A,B), Corrected sagittal view CBCT of one patient of one group at closed and opened position, showing condylar head of TMJs moves anterior and superior to the tip of articular eminence on MMO**, (C,D)** corrected sagittal view CBCT of one patient of the other group at close and open position, showing condylar head of TMJs moves anterior and superior to the tip of articular eminence on MMO

Prolotherapy Technique

The skin surface of the pre-auricular area was disinfected with betadine surgical scrub solution. The anatomic landmarks were located by asking the patient to open widely typically; each joint had 4 injection sites:● In the superior capsular attachment on the lateral margin of the glenoid fossa, 0.8 mL of the solution was slowly injected ● In the inferior capsular attachment on the condylar neck, 0.8 mL of the coded solution was injected.

The needle was then directed superficial to the TMJ capsule, and 0.4 mL of the solution was deposited. ● The superior joint space was approached with the needle directed superiorly and anteriorly toward the apex of the fossa, where contact was made with the periosteum. A spacer measuring about 1 cm was placed between the anterior teeth to allow access to the superior joint space,as well as to stabilize and fix the condylar position on the operated side during injection. Often, slight momentary resistance was felt as the needle penetrated into the joint capsule. One millilitre of the coded solution was slowly injected into the superior joint space .Postoperatively, the patients were asked to reduce or stop other pain medications and therapies that they were using as much as the pain would allow. They were also instructed to ingest only a soft diet for 2weeks to decrease the effort of the TMJ. TMJ pain as expressed by a verbal scale noting no, mild, moderate, or severe pain on palpation; maximal mouth opening (MMO) as measured by the distance in centimeters between the incisal edges of the upper and lower incisors; clicking sound; and frequency of luxations (number of locking episodes per week)were assessed by the same blinded operator at each injection appointment just before the injection procedure and one year after the last injection.

III. Results:

All patients tolerated the TMJ injection well without serious compli-cations. Discomfort after injection did not appear to vary between groups. Seven patients in each group had mild pain after injection. After the first injection, six patients in the active group and two in the placebo group complained of an itching sensation at the site of injection. This sensation disappeared spontaneously after a few days without any treatment. Some patients had transient facial palsy due to the anesthetic inclusion in the injected solution. The anesthetic effect diminished within 60 to 90 minutes postoperatively.

A) Pain on function:*Table (1)* summarize the comparison between two groups of TMJ pain on function throughout the study intervals as scored through VAS by the patients. Pain in function scored (8.1±2.1) pre-operatively in prolotherapy group, however, in the saline group scored (8.2±2.2). After the one year follow-up period, pain on function scored by (VAS) in prolotherapy group decreased to (3.2±0.58), similarly, the saline group scored (3.4±0.63), although, there was statistically significant decrease in pain scores (VAS) in both groups throughout the follow periods, there was no significant difference between groups at each follow-up intervals.

B) Numbers of locking:*Table (2)* illustrate the comparison between two groups in the numbers of jaw locking per week throughout the study period. Number of locking per week pre-operatively scored in prolotherapy group (3.24±0.47), whereas, the saline group scored (3.1±0.62). After one year post-operatively, the numbers of locking per week in prolotherapy group (0.04±0.01), and the saline group scored (0.06±0.015). There was no significant difference between group regard all times but there was significant decrease at both groups.

C) Maximum mouth opening (MMO): The comparison between two groups in the evaluation of the changes in the MMO in mm is shown in ***(Table 3).*** Maximum mouth opening in prolotherapy group scored pre-operatively (51.3±11.9), where the saline group scored (50.2±10.9). After one year post-operatively, maximum mouth opening in prolotherapy group scored(42.8±9.3), while the saline group scored (43.7±7.4). There was no significant difference between group regard all times but there was significant decrease at both groups.

Table (1): T.M.J Pain on function by VAS distribution between studied groups in a comparison table

	Prototherapy group	Saline group	t	P
Pre-operative	8.1±2.1	8.2±2.2	0.088`	0.99
One week post-operative	5.3±1.12	5.6±1.34	0.132	0.84
Two week post-operative	5.1±1.05	5.2±0.95	0.097	0.99
Third week post-operative	4.6±0.85	4.8±0.77	0.141	0.81
One month post-operative	4.1±0.73	4.4±0.98	0.135	0.83
One year post-operative	3.2±0.58	3.4±0.63	0.1	0.87

Table (2): Changes by time in numbers of individuals suffering of locking between studied groups in a comparison table.

	Prototherapy group	Saline group	t	P
Pre-operative	3.24±0.47	3.1±0.62	`0.24	0.71
One week post-operative	1.46±0.35	2.1±0.44	1.09	0.21
Two week post-operative	1.16±0.26	1.5±0.42	0.35	0.64
Third week post-operative	0.9±0.22	1.1±0.31	0.27	0.69
One month post-operative	0.7±0.16	0.8±0.27	0.17	0.84
One year post-operative	0.04±0.01	0.06±0.015	0.11	0.81

Table(3): Changes by time in maximum mouth opening distribution between studied groups in a comparison table.

	Prototherapy group	Saline group	t	P
Pre-operative	51.3±11.9	50.2±10.9	`0.27	0.77
One week post-operative	47.6±13.9	48.7±12.2	0.21	0.81
Two week post-operative	46.2±10.9	48.1±11.1	0.54	0.43
Third week post-operative	45.7±9.8	47.3±8.7	0.42	0.63
One month post-operative	43.2±10.7	45.8±11.4	0.87	0.29
One year post-operative	42.8±9.3	43.7±7.4	0.52	0.44

IV. Discussion

In the present study, dextrose was selected as the main ingredient in the solution because it is the most common proliferant used in prolotherpy, is readly available and inexpensive when compared to other proliferants and has a high safety profile **(18)**

Various concentrations of dextrose ranging between 10% and 50% have been used in treatment of TMJ hypermobility in different studies. concentration of dextrose. **(19)**

Hakala and Ledermann(20) believed that the precise concentration of dextrose is not critical so long as it is strongly hypertonic and causes adequate cell wall lysis to attract fibroblasts and begins the regenerative process. **Mustafa et al., (21)** advised that 10% dextrose can be sufficient in TMJ hypermoblity treatment.

The present study applied dextrose prolotherapy with concentration of 10% injected in 4 different sites : superior joint space, superior, inferior capsular attachments and superfacial around capsule at 3sessions monthly intervals for study group patients , however , in control group , the patients was injected with saline injected in the same sites and within the same intervals sessions

The study group in the present study showed a statistically significant decrease in pain intensity through all the study periods, although the results obtained were not significantly superior to those recorded in placebo group, this result was in agreement with studies of **Kilic et al.(12) Refai et al.(13,22)), Mustafa et al.,(21).Cezairli et al.,(23)**using dextrose prolotherapy and saline for management TMJ hypermobility.

The mean value of locking number per week between the study and placebo groups between intervals was reduced in two groups however. Both groups showed statically significant decrease in numbers of locking after two weeks followed by insignificant decrease after third weeks, one month and one year. There was no significant difference between group regard all times but there was significant decrease at both groups there were slight improvement in active group than placebo group which was not significant, this results was in agreement with the results of **Kilic et al.(12) Refai et al.,(13)) and Mustafa et al.,(21)**.

There was a significant improvement in MMO the three measurements which showed significant reduction throughout the study period in MMO, in active and placebo groups, these results were not comparable with the results of **Refai et al.,(13)** who showed significant decrease in the measurements in the study group than placebo group , this difference might due to the number of patient that contributed in the two studies , 30 patients contributed in the present study while 12 patients contributed in the study of **Refai et al.,(13)** which was not sufficient enough to confirm the results , however , the results was in agreement with the results of **Kilic et al.,(12)Mustafa et al.,(21)**.

The post operative Cone Beam Computed Tomography within our study showed that no changes in the condylar position in maximum mouth opening, this result was in agreement with the study of **Refai et al. (22)**

Several molecules have been recognized as potential 'proliferants' and it has been suggested that the mechanism of action by which they induce local inflammation might vary depending on the type of molecule. Theoretically, potential 'proliferants' can be classified into three groups based on their possible biochemical mechanisms: irritants, osmotics, and chemotactics. Concentrated dextrose is one of the osmotic shock agents, and acts by dehydrating cells at the injection site. This leads to local tissue trauma, which in turn might attract granulocytes and macrophage**(12)**

It is presumed that prolotherapy may trigger an immune response, activating granulocytes and macrophages to release growth factors sufficient to stimulate cell growth or cell production, leading to fibroblast proliferation followed by matrix production and collagen deposition. The new collagen undergoes contraction, pulling the 'loosened' ligament and tendon tighter.**(12)**

Several authors believe that the similar and profound improvements observed after saline or dextrose injections do not result from the injections themselves, but rather from needle trauma and micro-bleeding. It has been well documented by some authors that cell membrane disruption caused by a needle will stimulate the release of pro-inflammatory lipids from cell membranes, and that these lipids produce growth factors.**(24)** Others believe that needle contact can result in micro-bleeding, and that blood contains a number of growth factors.**(24)**
According to **Yelland et al.,** the use of a needle alone may be beneficial in patients with chronic lower back pain.**(25)** These authors observed that the patients injected with dextrose appeared to fare somewhat better than

patients injected with saline, but the difference was not significant and the patients in both groups experienced significant and sustained benefits.

As a result, within the limits of this study, it was determined that prolotherapy may lead to significant reduction in mouth opening, lateral , protrusive movements and pain associated with TMJ hypermobility, however ,prolotherapy has no superiority over placebo in improving TMJ hypermobility ,which was in agreement with many studiesof **Kilic et al.,**[(12)] **Refai et al.,**[(13)] **and Mustafa et al.**[(21)].

Compliance with Ethical Standards:

Funding No funding received **Conflict of interest** The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the clinical standards of the institutional and /or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

Informed consent Informed consent was obtained from all individual participants included in the study

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