



Botulinum Toxin Versus Dextrose Prolotherapy: Which is More Effective for Temporomandibular Joint Subluxation? A Randomized Clinical Trial

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Purpose: Botulinum toxin type A (BTX-A) therapy or dextrose prolotherapy (DP) has been used to treat temporomandibular joint (TMJ) disorders. However, the superiority of one method over the other has not been studied in patients with TMJ subluxation. Therefore, this study aims to answer the following clinical question: among patients with TMJ subluxation, do those undergoing BTX-A injection into lateral pterygoid muscles, compared to those undergoing intra- and periarticular DP injections, have better outcomes in terms of locking episodes and patient satisfaction?

Methods: A randomized clinical trial was implemented in adult patients with TMJ subluxation. The sample was composed of patients with TMJ subluxation with painful open-locking during wide mouth opening and/or yawning at baseline. The subjects were treated randomly with one of two treatment techniques with equal numbers as follows: one-session BTX-A injection into lateral pterygoid muscles (BTX-A group) or three sessions of dextrose injections around TMJ (prolotherapy group). The predictor variable was the treatment technique (BTX-A or prolotherapy injections). The primary outcome variable was the frequency of locking episodes. The secondary outcome variable was patient satisfaction. The primary outcome variable was recorded at baseline and 8-12 months following the injections. The secondary outcome variable was recorded only 8-12 months following the injections. Descriptive and bivariate statistics were computed. The data were analyzed with the Wilcoxon and Mann-Whitney *U* tests.

Results: The baseline sample was composed of 30 patients with TMJ subluxation. However, the follow-up sample comprised 25 subjects: 11 (9 females, 2 males; 25.64 years) in the BTX-A group and 14 (10 females, 4 males; 32.37 years) in the prolotherapy group. Locking episodes decreased significantly in the two groups with no significant difference ($P < .01$). Seven patients in the BTX-A group (7 of 11 patients; 63.6 percent) and eight (8 of 14 patients; 57.1 percent) in the prolotherapy group reported no complaint of locking at the end of follow-up, with no significant difference between the groups ($P > .05$). Patient satisfaction showed no significant difference between the groups ($P > .05$).

Conclusion: These findings suggested that BTX-A injection is no more effective than DP for any outcome variables of TMJ subluxation assessed.

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Temporomandibular joint (TMJ) subluxation is a hypermobility disorder that involves condyle-disc complex and articular eminence. It is a condition where the mandibular condyle moves beyond the articular eminence during a wide mandibular opening. It catches in an open position before the condyle returns to the fossa.^{1,2} When the mandible opens to its fullest extent, a temporary pause occurs, followed by a sudden jump or leap to the maximally open position. This jump produces a noise like a thud, not a click. According to the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD), the jaw can close spontaneously, or the patient has to do a self-manuever to close the jaw.^{2,3} This condition is called subluxation or hypermobility.^{1,2}

The cause of TMJ subluxation is usually not pathologic and is mainly associated with the morphological structure of the joint. TMJ subluxation is more likely to occur in patients whose articular eminence has a short, steep posterior slope followed by a longer, flatter anterior slope. Other causes are elongation of the ligaments, internal derangement and disc interference disorders, occlusal disturbances, and joint laxity.^{2,3}

Prolotherapy-repeated injections of an irritant dextrose solution, has been used to treat several joint and muscle pains and headaches.⁴ The efficacy of dextrose prolotherapy (DP), including varying dextrose concentrations and sessions for managing TMJ hypermobility (subluxation) or recurrent dislocation, has been evaluated in several studies.⁵⁻¹¹ A few studies assessed botulinum toxin type A's (BTX-A) effects on treating TMJ disorders and pain.¹²⁻¹⁴ A recent study¹² reported that a single injection of BTX-A presents long-term results up to 72 months in reducing pain in persistent myofascial temporomandibular disorder pain patients.

Intra- and periarticular DP injections have been used to manage TMJ hypermobility or subluxation. To date, no study evaluated the effects of BTX-A injection on locking episodes and satisfaction of patients with TMJ hypermobility or subluxation. In addition, the superiority of one method over the other has not been studied in patients with TMJ subluxation.

This study aimed to answer the following clinical question: among patients with TMJ subluxation, do those undergoing BTX-A injection into lateral pterygoid muscles, when compared to those undergoing intra- and peri-articular DP injections, have better outcomes in terms of locking episodes and patient satisfaction? The authors hypothesize that one BTX-A injection into lateral pterygoid muscles will produce better clinical outcomes in locking episodes and patient satisfaction than three intra- and periarticular DP injections. This study had two specific aims as: 1) to measure and compare the frequency of locking ep-

isodes before and after the treatment, and 2) to measure and compare post-treatment patient satisfaction in patients with TMJ subluxation treated with one BTX-A injection into the lateral pterygoid muscles or three intra- and periarticular DP injections.

Materials and Methods

STUDY DESIGN AND SAMPLE

To address the research purpose, the author designed and implemented a prospective randomized clinical trial composed of patients with TMJ subluxation who underwent 1 of the 2 TMJ subluxation management protocols at the Faculty of Dentistry of Atatürk University. The ethics committee of the faculty approved the study design (Approval Number is 2014/11). Before participating in the study, each subject signed informed consent. Helsinki Declaration guidelines are followed in this randomized clinical trial.

Patient selection was mainly based on TMJ subluxation resulting in painful open-locking and complaints of disturbing joint noise during wide mouth opening and/or yawning. The diagnosis of TMJ subluxation was based on the patient's history and clinical assessment of an abnormally moving condyle, which slides just anterior to the eminence and then returns to the glenoid fossa by active jaw manipulation of the patient or self-reduction.

The study population comprised all patients presenting for the evaluation and management of TMJ subluxation from January 2013 through May 2014. To be included in the study sample, patients had to meet the following criteria: 1) adequate existing clinical data at baseline and the postoperative interval (follow-up); 2) TMJ subluxation without degenerative joint signs (diagnosed with cone-beam computed tomography or magnetic resonance imaging and clinically); 3) complaints of joint sounds, dislocation, and facial pain; 4) age > 16 years; and 5) completion of 1 of the two management protocols for the TMJ subluxation.

Patients were excluded from the study sample if they had hematologic or neurologic disorders, inflammatory or connective tissue disease, widespread disorders of muscle activity, malignant disease in the head and neck region, pregnancy, a history of drug allergy, immunosuppressive drug intake, degenerative TMJ disorders, previous TMJ treatment or craniofacial surgery, the existence of inflammation or infection at the injection areas, or inadequate existing at baseline and the postoperative interval (follow-up).

Thirty patients were assigned randomly into one of the two treatment groups in equal numbers. Participants in group 1 (BTX-A group) received one session of BTX-A injection into lateral pterygoid muscles. In the prolotherapy group (group 2), participants

received three sessions of intra- and periarticular DP injections, with accordance to the method previously described by Cömert Kiliç and Güngörmüş.⁶ Briefly, the subjects in this group received 1 ml injection of dextrose solution (2 ml 30% dextrose + 2 ml saline + 1 ml 2% articaine or mepivacaine) per injection area (posterior disk attachment, superior joint space, superior and inferior capsular attachments, and stylomandibular ligament) three times, each a month apart (Fig 1). The local anesthesia in the injected solutions was used for the postinjection comfort of the patients.

Analgesic drugs (Paracetamol) were recommended after the injections for possible pain complaints.

STUDY VARIABLES

The predictor variable was the treatment technique (BTX-A or prolotherapy injections). The other predictor variables were the age and sex of the subjects. Therefore, the age and sex of the subjects were recorded, and the relationship of these variables with the predictor variable was considered for statistical analysis.

The primary outcome variable was the frequency of locking episodes. The primary outcome variable was

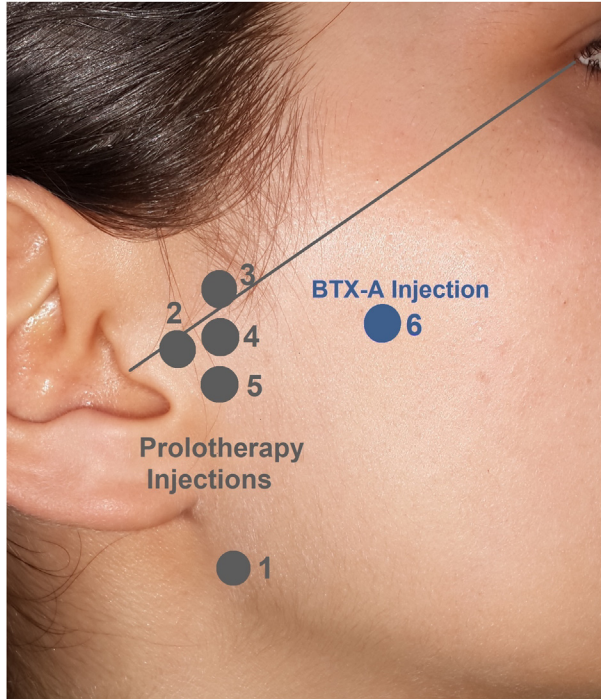


FIGURE 1. Injection points of dextrose prolotherapy: (1) stylomandibular ligament, (2) posterior disk attachment, (3) superior capsular attachment; (4) superior joint space, (5) inferior capsular attachment; and injection point of BTX-A: into the space formed by the zygomatic arch - the sigmoid notch of the mandible (6).

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recorded at baseline and 8-12 months following the injections. The frequency of locking episodes was rated with five grading levels (0, never; 1, seldom; 2, sometimes; 3, often; and 4, always), and these levels were used for statistical analysis.

The secondary outcome variable was patient satisfaction. Patient satisfaction was recorded after only 8-12 months following the injections. Patient satisfaction included five grading levels: 1 = no; 2 = lessen; 3 = moderate; 4 = good; and 5 = excellent satisfaction.

BTX-A THERAPY

The BTX-A (BOTOX®, Allergan, Turkey) was provided as a freeze-dried powder of 100 units, and it was prepared gently with 1 ml of sterile saline solution, with a concentration of 10 U/0.1 ml. BTX-A was used immediately after preparation. The skin surface was disinfected with a povidone-iodine solution. Solutions were drawn into 1 cc tuberculin syringe with a 30 gauge needle. Extraoral 40 U BTX-A injections were given into both lateral pterygoid muscles according to the injection method previously described by Fu et al.⁵ The extraoral injection was made into the space formed by the zygomatic arch - the sigmoid notch of the mandible, 1 cm below the central zygomatic arch during the mandible was in a normal position and the mouth closed. The needle was advanced at right angles to the skin at a depth of 3-4 cm⁵ (Fig 1). The syringe was aspirated to ensure that the tip was not inside a blood vessel before 40 U BTX-A was injected into the muscle. After the applications, water contamination during a few hours in injection areas was prohibited.

DATA ANALYSIS

The sample size of this study was calculated with a significance level of 0.05 and 90% power. A clinically meaningful 80 percent decrease in the frequency of locking episodes after the treatment is considered for power analysis,⁷ and this analysis showed at least 11 patients in each group. More patients were included in the two groups (15 subjects in each group) to increase the study's power and compensate for possible dropouts during the planned study period.

All statistical analyses were conducted using the SPSS (Statistical Package of Social Sciences, Chicago, IL) for Windows software program version 17.0. A *P*-value of less than .05 was considered statistically significant. Intragroup comparisons for both groups were performed using the Wilcoxon test. In addition, changes in the frequency of locking episodes in each patient were recorded, and the data were used for intergroup comparisons using the Mann-Whitney *U* test.

Table 1. BIVARIATE ASSOCIATIONS BETWEEN STUDY AND PREDICTOR VARIABLES AT BASELINE (GROUP 1, BTX-A; GROUP 2, PROLOTHERAPY)

Study variable	Predictors		P Value
	Group 1 (n = 11)	Group 2 (n = 14)	
Age (y)	25.64 ± 7.35	32.36 ± 13.45	.05*
Women (%) [‡]	9 (81.8%)	10 (71%)	.05 [†]
Follow-up period (m)	8.64 ± 2.29	11.71 ± 1.14	.01*
Mean frequency of locking episodes	3.10 ± 1.22	2.50 ± 1.23	.05 [†]

* Independent t-test.

[†] Mann-Whitney U test.

[‡] Number of women (total percentage of women in sample).

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Results

At baseline, thirty subjects were included in the study: fifteen in the BTX-A and prolotherapy groups. Five patients were excluded from the study due to the absence of data after the follow-up period: four in the control group and one in the prolotherapy group. The final study sample consisted of 25 patients. These patients had a mean age of 29.40 ± 11.50 years (16 to 56 years). The BTX-A group consisted of 11 patients (nine females and two males), and the prolotherapy group consisted of 14 patients (ten females and four males). The frequency of locking episodes was seen seldom in 2 patients, sometimes in 1 patient, often in 2 patients, and always in 6 patients in the BTX-A group. In the prolotherapy group, the frequency of locking episodes was seen seldom in 4 patients, sometimes in 3 patients, often in 3 patients, and always in 4 patients.

All patients complained of disturbing joint noise and TMJ subluxation with painful open-locking during wide mouth opening and/or yawning at baseline. The severity of locking episodes was prominent in the BTX-A group.

No significant difference at baseline was observed between the two groups of patients for all study variables, including mean age, gender, and mean frequency of locking episodes, except the follow-up period. The mean age was 25.64 ± 7.35 years in the BTX-A group and 32.37 ± 13.45 years in the prolotherapy group ($P > .05$). The mean postoperative follow-up period was 8.64 ± 2.29 months in group 1 and 11.71 ± 1.14 months in group 2 ($P < .01$). The mean frequency of locking episodes was 3.10 ± 1.22 years in the BTX-A group and 2.50 ± 1.23 in the prolotherapy group ($P > .05$) (Table 1).

Intragroup comparisons of the primary outcome variable showed that the frequency of locking episodes decreased significantly in both groups (Table 2).

Comparison of the changes from the follow-up to baseline outcomes in primary outcome variables between the two groups showed that one group was not more effective than the other group for locking episodes ($P > .05$.) Seven patients in the BTX-A group (7 of 11 patients; 63.6 percent) and eight (8 of 14 patients; 57.1 percent) in the prolotherapy group reported no complaint of locking at the end of follow-up. The remaining three patients (27.3 percent) reported remission in locking episodes, and one (9.1 percent) reported no change in the BTX-A group. Two patients (14.3 percent) reported remission of locking episodes, and 4 (28.6 percent) reported no change in locking episodes during the follow-up period in the prolotherapy group (Table 3).

Patient's pleasure scores (satisfaction degree) were reported during the follow-up period, and between-group comparisons are shown in Table 3. In the BTX-A group, two patients reported excellent, seven reported good, and one reported moderate satisfaction at the end of the follow-up. In the prolotherapy group, five patients reported excellent, five reported good, two reported moderate, and one reported lessened satisfaction at the end of follow-up. One patient reported no satisfaction change in both groups. 81.8 percent of patients in the BTX-A group and 71.4 percent in the prolotherapy group reported their high pleasures (good plus excellent), respectively. Patient satisfaction showed no statistically significant difference between the groups ($P > .05$) (Table 3).

Discussion

DP has been used for the management of TMJ hypermobility or subluxation. No study evaluated the effects of BTX-A injection on locking episodes and satisfaction of patients with TMJ hypermobility or subluxation. In addition, the superiority of one method over the other has not been studied in patients with TMJ subluxation.

Table 2. INTRA-GROUP COMPARISONS OF OUTCOME VARIABLES ASSESSED BY WILCOXON SIGNED RANK TEST (GROUP 1, BTX-A; GROUP 2, PROLOTHERAPY)

Variable	Groups	Grading Levels	Preoperative	Follow-Up	P Value
Frequency of locking episodes	Group 1 (n = 11)	never	-	7 patients	.01
		seldom	2 patients	2 patients	
		sometimes	1 patient	1 patient	
		often	2 patients	-	
		always	6 patients	1 patient	
	Group 2 (n = 14)	never	-	8 patients	.01
		seldom	4 patients	3 patients	
		sometimes	3 patients	3 patients	
		often	3 patients	-	
		always	4 patients	-	

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The present randomized clinical trial was conducted to investigate and compare the treatment outcomes of TMJ subluxation treated with three sessions of intra- and periarticular injections of DP versus one session of BTX-A injection into the lateral pterygoid muscle. The authors hypothesized that the BTX-A injection would be more effective than the repeated injections of irritant dextrose solution. Pretreatment (baseline) bivariate associations between the study and predictor variables confirmed no statistically significant difference in the predictor variables, including age, gender, and mean frequency of locking episodes. Only the follow-up period in the prolotherapy group is greater than that in the BTX-A group ($P < .01$). The existence of 3 months of difference in the follow-up period may produce some concerns. However, our experience revealed that similar outcomes occurred after the follow-up period of 6 months in both groups when patients followed 3-month intervals after then. This experience also supported the findings of the other studies.⁵ Therefore, any variable potentially affecting the outcomes was eliminated at the beginning of the study, and the two treatment techniques used for TMJ subluxation remained the primary predictor variables. The primary outcomes in the two groups disproved the authors' hypothesis, because the mean change in outcome variables showed no statistically significant difference between the two groups ($P > .05$). These results suggest that one session of BTX-A injection was no more effective than DP for locking episodes and patient satisfaction than three sessions of sclerosing dextrose injections in treating these patients with TMJ subluxation (Table 3). A secondary outcome of the present study was that both treatment techniques significantly improved the primary and secondary clinical outcomes (Tables 2 and 3).

These outcomes might be explicable when the biological and clinical effects of BTX-A injection or DP are considered.

BTX-A has more than one serotype and a powerful impact. It contains clostridium botulinum toxin that reversibly blocks presynaptic acetylcholine release at the neuromuscular junction. The blocking effects of the toxin on the release of acetylcholine from motor nerve endings result in dose-dependent weakness of the muscle(s) injected and lower muscle tone.¹⁵ It proves muscle relaxation and reduces muscle vessel compression.¹⁵ Due to its muscle activity reduction and pain relief effects, BTX-A has emerged as a potential therapy for TMD, with available clinical reviews supporting its benefit in treating TMD. Some researchers^{4,5} reported improvements in dislocations after BTX-A injection into the lateral pterygoid muscle. Bouso et al reported that three of four patients did not present any episode of TMJ dislocation after the treatment and during the observation period between 5-10 months. Fu et al reported no dislocation after the treatment and 3-24 months observation periods, except only one patient presented dislocation on the second day after injection. Zeigler et al¹⁶ considered a follow-up between 6 months to 4 years in patients with TMJ dislocation treated with BTX-A injection. We observed a considerably high success rate two-three weeks after the injection in the BTX-A group. We also found an approximately 90 percent success rate in this group when considering patients' reports of no locking episodes or remission of episodes at the end of the follow-up.

Patients with TMD experienced reduced pain, bite force, and increased mouth opening following BTX-A injection.^{12,17} Pain reduction may be associated with the direct action of BTX-A on muscular contraction. Pain reduction also may be related to the dose-dependent anti-inflammatory effect of BTX-A. At least three mechanisms of BTX-A have been recognized. The first is muscle loosening, caused by the inhibition of alpha and gamma neurons. The second mechanism is based on a reduction of inflammation both within

Table 3. COMPARISON OF CHANGES IN CLINICAL OUTCOME VARIABLES BETWEEN THE TWO GROUPS ASSESSED BY MANN-WHITNEY U TEST (GROUP 1, BTX-A; GROUP 2, PROLOTHERAPY)

Variable	Group 1 (n = 11)	Group 2 (n = 14)	P Value
Locking Episodes			
No complaint of locking (complete healing)	7 patients (63.6%)	8 patients (57.1%)	.05
Remission of locking episodes	3 patients (27.3%)	2 patients (14.3%)	
No change of locking episodes (No healing)	1 patient (9.1%)	4 patients (28.6%)	
Satisfaction degree			
No	1 patient (9.1%)	1 patient (7.1%)	.05
Lessen	-	1 patient (7.1%)	
Moderate	1 patient (9.1%)	2 patients (14.4%)	
Good	7 patients (63.6%)	5 patients (35.7%)	
Excellent	2 patients (18.2%)	5 patients (35.7%)	

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the TMJ and the muscle. Inflammation of the TMJ, particularly the capsule and supporting ligaments, reduces the range of joint movements. The third mechanism is the relief of pain and the increase in the degree of mouth opening.^{14,15}

Some researchers^{7-10,18} reported that dextrose injections have a significant healing effect in many clinical parameters in the short and long term, and these findings support the results of the present study. Refai⁹ reported substantial and stable improvements in patients with TMJ hypermobility (subluxation) during the long-term observation period. They reported that approximately 90 percent of the patients showed no complaint of locking after the end of the study. Majumdar et al¹⁸ reported a success rate of 91.3 percent with a minimum follow-up period of 13.9 months after the TMJ hypermobility with dextrose injections. Zhou et al⁸ reported an overall success rate of 91% (41/45 patients) when they regarded the absence of further subluxation for more than 6 months. Ungor et al⁷ reported a significant decrease in pain during TMJ function and diminished TMJ locking during the follow-up period in patients with TMJ dislocation. These authors reported that none of the patients presented luxation from the 12th to the 24th week after the surgery, and 9 of 10 patients showed decreased locking episodes after the first injection. In our study, we found that 71 percent of patients reported no locking or remission of episodes at the end of the follow-up in the prolotherapy group.

Different dextrose concentrations ranging from 10 to 50% have been used to treat TMJ dislocation.^{8,19} However, more than 10% dextrose concentration is recommended for effective treatment, and we preferred a 12.5% dextrose concentration due to its inflammatory capacity. In the recent study by Refai,⁹ 61 patients with TMJ subluxation (hypermobility) underwent

four sessions of intra-articular and periarticular dextrose injections composed of 10% dextrose/mepivacaine solution. The results confirmed no change in condylar position and joint cartilage following dextrose injections but permanent improvements in clinical parameters.

Irritants, osmotics, and chemotactics are potential proliferants due to their possible biochemical mechanisms. Concentrated dextrose is one of the osmotic shock agents, and it acts by dehydrating cells at the injection site. Injection of concentrated dextrose leads to local tissue trauma in the injected area, which may attract granulocytes and macrophages. 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/tendon tighter.⁶ Many studies¹⁷ have demonstrated that concentrated dextrose has the potential to increase inflammatory markers, enlarge areas in collateral ligaments, and stimulate the release of growth factors, including platelet-derived growth factor, transforming growth factor beta, and insulin-like growth factor. Prolotherapy may activate granulocytes and macrophages by releasing growth factors. It may stimulate the growth and production of cells and prove fibroblast proliferation with collagen and matrix production.²⁰ On the other hand, some other authors¹⁰ claimed that the positive effects observed after DP injections resulted from needle trauma and micro-bleeding not from the injected solution.

The patients with TMJ hypermobility treated with DP followed short- and/or long-term periods.⁷⁻¹⁰ Ungor et al⁷ and Mustafa et al¹⁰ followed their patients

for 1 month and 6 months after the last dextrose injection, respectively. On the other hand, Refai et al⁹ followed their patients with short- (3 months) and long-term (1-4 years) follow-up periods.

Some limitations exist in this study. This study design had a subjective evaluation (satisfaction score). In addition, although the sample size of our study was calculated using power analysis and is adequate to detect meaningful differences between the groups, the relatively small sample size for the study limits the broader generalizability of the findings.

These findings suggested that BTX-A injection is no more effective than DP for any outcome variables of TMJ subluxation assessed.

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