Treatment of Temporomandibular Dysfunction With Hypertonic Dextrose Injection (Prolotherapy): A Randomized Controlled Trial With Long-term Partial Crossover

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Abstract

Objective: To assess the efficacy and longer-term effectiveness of dextrose prolotherapy injections in participants with temporomandibular dysfunction.

Patients and Methods: A randomized controlled trial with masked allocation was conducted from January 14, 2013, through December 19, 2015. Forty-two participants (with 54 joints) meeting temporomandibular dysfunction criteria were randomized (1:1) to 3 monthly intra-articular injections (20% dextrose/0.2% lidocaine or 0.2% lidocaine) followed by as-needed dextrose/0.2% lidocaine injections through 1 year. Primary and secondary outcome measures included a 0 to 10 Numerical Rating Scale score for facial pain and jaw dysfunction; maximal interincisal opening (MIO) measured in millimeters, percentage of joints with 50% or more change (improvement) in pain and function, and satisfaction.

Results: Randomization produced a control group with more female participants (P = .03), longer pain duration (P = .01), and less MIO (P = .01). Upon 3-month analysis, including pertinent covariates, dextrose group participants reported decreased jaw pain (4.3 ± 2.6 points vs 1.8 ± 2.7 points; P = .02), jaw dysfunction (3.5 ± 2.8 points vs 1.0 ± 2.1 points; P = .008), and improved MIO (1.5 ± 4.1 mm vs −1.8 ± 5.1 mm; P = .006). Control group participants received dextrose injections beginning at 3 months. No between-group differences were noted at 12 months; pooled data suggested that jaw pain, jaw function, and MIO improved by 5.2 ± 2.7 points (68%), 4.1 ± 2.8 points (64%), and 2.1 ± 5.5 mm, respectively. Pain and dysfunction improved by at least 50% in 38 of 54 (70%) and 39 of 54 (72%) jaws, respectively.

Conclusion: Intra-articular dextrose injection (prolotherapy) resulted in substantial improvement in jaw pain, function, and MIO compared with masked control injection at 3 months; clinical improvements endured to 12 months. Satisfaction was high.

Trial Registration: clinicaltrials.gov Identifier: NCT01706172
described in the Research Diagnostic Criteria for Temporomandibular Dysfunction (RDC/TMD) evaluation tool (myofascial, disc displacements, and other joint conditions), the suggested initial management is similar for all 3 groups and includes use of an analgesic, such as an oral or a topical nonsteroidal anti-inflammatory drug (NSAID), and an occlusal splint. A group-specific treatment approach is limited by several factors, including an overlap between diagnostic groups with assignment of the same joint to more than 1 group, poor understanding of biological pain mechanisms for each group, and insufficient high-quality clinical evidence to guide treatment. For example, occlusal modification, which has been a mainstay of treatment for decades, is not supported by a systematic review of prospective studies. Considering that surgical management should be used as an exception, a conservative treatment approach that is reliable, cost-effective, and accessible to primary care practitioners or dentists is needed. Injection of dextrose to treat chronic musculoskeletal pain (dextrose prolotherapy [DPT]) is supported by numerous randomized studies and systematic reviews. At the inception of the present study, the efficacy of DPT for TMD had been reported in 1 small (n=12) randomized trial by using a method targeting both intra-articular and extra-articular sites. Intrarticular—only injection of the temporomandibular joint (TMJ) for TMD has been recommended for reproducibility and simplicity and is commonly used. We tested the hypothesis that DPT using an intra-articular—only protocol will result in significant improvement in TMD pain and dysfunction and increase maximal interincisal opening (MIO).

PATIENTS AND METHODS
This study was approved by the Clinical Research Ethics Board of the University of British Columbia (ClinicalTrials.gov identifier: NCT01706172). Inclusion criteria were adults aged 19 to 80 years with moderately severe and chronic (>3 months) pain and jaw dysfunction, indicated by a score of “6” or more on a 0 to 10 Numerical Rating Scale (NRS), in which 0 meant “no pain or dysfunction” and 10 “the worst pain or dysfunction imaginable. Dysfunction was defined as “difficulty chewing, jaw fatigue with eating, tension in jaw, or grinding of teeth.” Exclusion criteria included allergy to lidocaine, dental problems, or sinus pathology potentially contributing to pain, pain in any other anatomical site persistently greater than that in the TMJ area, long-term intake of NSAIDs or corticosteroids, or active rheumatological conditions. Interested individuals underwent initial telephone screening using a scripted interview, with those meeting our inclusion/exclusion criteria further screened in the office to confirm eligibility, to obtain consent, and for enrollment in the study. For each prospective participant, both TMJs were assessed separately for eligibility.

Screening, Allocation, and Randomization
The office manager performed the phone screening interview and scheduled the physical examination. Eligibility was determined after the examination by the primary investigator (W.F.L.). A research assistant, who did not interact with patients and did not participate in patient scheduling, randomly assigned candidates to 1 of 2 blinded injection groups (20% dextrose/0.2% lidocaine or 0.2% lidocaine) by using a computer-generated password-protected randomization scheme in forced blocks of 20. Randomization (1:1) was by participant, so the same solution was used for both sides in the same participant if both TMJs were included. The order of appointments, eligibility determination, and group assignment were recorded and retrospectively compared with the original computer-generated randomization schedule to confirm sequential allocation. Participants, office manager, and the primary investigator/injector (who was also the outcome assessor) were masked to injection group allocation.

Injection Intervention
Masked injections were performed at 0, 1, and 2 months. The treatment syringe was prepared by the research assistant, according to allocation assignment, in a room separate from the participant and the primary
investigator/injector. Solutions were mixed using a back and forth motion to distribute the solutions and avoid any visible “swirling” of the more viscous 50% dextrose solution inside the syringe. The needle was attached before handling by the injector to limit glove contact with dextrose solution and thereby avoid appreciation of any slight stickiness of the dextrose solution.

This is a closed-mouth approach with the jaw relaxed; ultrasound was not used. The point of needle entry was 1 cm below the apex of the zygomatic arch (Figure 1), with a 45° cranial and 10° posterior angulation measured using a 1-in 30-G needle (Figure 2). If needle contact occurred, it was considered to be condylar contact and a more cranial angulation was used. A 10° posterior angulation was used to direct the needle tip most consistently into the superior joint space, as the needle entry point is typically anterior to the condyle. One milliliter of solution was injected in each affected joint, with a free flow of fluid after preinjection aspiration. Before this clinical study, informal observations of ultrasound-monitored TMJ injection by 1 (S.K.H.L.) of the coauthors confirmed the angles used in this study and that a 1-in 30-G needle has adequate length to reach the intra-articular space despite variations in body habitus.

Patients were advised to use acetaminophen or NSAIDs as well as local application of ice for postprocedure pain. The procedure was repeated monthly for 2 months for a total of 3 injections. At 3-month follow-up, allocation groups were revealed; participants in both groups were offered open-label injection of 20% dextrose/0.2% lidocaine monthly on a by-request basis. The use of new oral devices and dental work for malocclusion was discouraged during the 12-month period of data collection.

Outcome Measures
The primary outcome measure was a score of pain intensity and severity of jaw dysfunction as assessed by two 0 to 10 NRSs (“Rate the maximal pain (or dysfunction) over the last 4 weeks.”). The NRS is commonly used to evaluate the effect of therapeutic interventions for TMD, with a 15% change (reduction) in the evaluation of chronic musculoskeletal pain reported as the minimal clinically important difference. We also calculated the percentage of joints with 50% or more improvement in pain or function, as this criterion has previously been associated with clinically important improvement in several musculoskeletal conditions. In participants with 2 eligible TMJs, NRS data were collected separately for each treated joint.

Maximal interincisal opening was measured in millimeters using the TheraBite device (available at www.craniorehab.com). Measurement of MIO has been reported to have a high interrater reliability in TMD. Treatment satisfaction was assessed at the 3-month follow-up visit before revealing allocation group with the question “On a scale from 1-5, please rate satisfaction with your results, where 1 means ‘no satisfaction’ and 5 means ‘complete satisfaction’.”
Demographic characteristics and classification of TMD type according to RDC/TMD version 1 were collected at baseline for participant characterization and used as covariates for statistical analysis.

Analyses

Unpublished data from 5 patients with TMD treated with 20% dextrose/0.2% lidocaine and 5 treated with 0.2% lidocaine were used for power analysis (Stanley K.H. Lam, MD, unpublished data, June 2012). Using a predicted between-group NRS difference of 2.4 points, an SD of 1.33, and an effect size of 1.8, 20 participants (10 in each group) would provide 90% power to detect a difference in mean NRS scores (pain or dysfunc-
tion) between dextrose and control groups at a significance of .025. We chose to enroll 20 participants in each group.

Data were analyzed using PASW Statistics 18, Release Version 18.0.0 (IBM Corp.). Analysis was performed by intention to treat. Descriptive statistics (expressed as mean ± SD) were calculated for outcome variables at each time point. Baseline between-group data were analyzed for significant differences by t tests for nominal variables and Pearson chi-

![CONSORT flow diagram](https://example.com/consort_flow_diagram.png)

FIGURE 3. CONSORT flow diagram. aControl injection = sterile water + 0.2% lidocaine. bDextrose injection = 20% dextrose + 0.2% lidocaine. cTwo participants, each with 2 qualifying joints, dropped out of the study. Both were from the dextrose group. One participant withdrew because of increasing pain and swelling at 2-month follow-up after having received 2 injections of dextrose and was subsequently diagnosed with a parotid tumor. The second participant moved internationally after 1 treatment. Data on pain at 2- and 1-month follow-up, respectively, and maximal interincisal opening at baseline were carried forward in the analysis, and satisfaction was estimated at 1 of 5 (no satisfaction).
square tests for categorical variables. Baseline characteristics were included in the model as covariates. Analyses of covariates were applied to compare the groups for magnitude of change in the 0 to 10 NRS pain score and 0 to 10 NRS function score between baseline and each follow-up time point (1, 2, 3, and 12 months) and for magnitude of change in MIO between baseline and 3 and 12 months. A 2-tailed $P$ value of less than .05 was established as the statistical significance level. A $t$ test was performed to compare between-group satisfaction scores at 3 months. In order to test for a between-RDC/TMC group effect on outcomes, a one-way analysis of covariance was used to compare dextrose and control effects on improvements in TMD pain and dysfunction scores at the 12 month follow-up point, while including the 3 RDC/TMD diagnostic groups as the covariates. Because MIO less than 40 mm is considered an indication of joint opening limitation, a $t$ test was performed to compare between-group improvement in MIO at 3 months in those who presented with an MIO of less than 40 mm. The long-term effect of treatment on MIO was evaluated by comparing the number of joints with an MIO of 40 mm or greater at 0 and at 12 months by using the Pearson chi-square test followed by a 1-sided Fisher exact test. Analysis of pain, dysfunction, and MIO data from participants who dropped out were managed using the “last value carried forward” approach.

### RESULTS

Adults from the community of Invermere, British Columbia, Canada, were recruited, beginning January 14, 2013, with last data collected on December 19, 2015. Of the 80 persons prescreened by telephone, 52 met TMD severity and duration criteria and were seen for further history taking and examination (Figure 3). Among these, 42 individuals with 54 qualifying joints met eligibility criteria and were enrolled and randomized. Two participants in the dextrose arm, each with 2 qualifying joints, left the study. One participant dropped out at 2 months (after 2 treatments) because of increasing jaw pain and jaw area swelling. She was diagnosed with an acinic cell tumor of the parotid gland. The second participant was lost to follow-up at 1 month because he or she had moved internationally after 1 treatment. The satisfaction score for both these patients was rated as 1 of 5 (no satisfaction). The remaining 40 participants with 50 eligible joints completed the 3-month double-blind treatment period and 9 months of open-label as-needed treatment and were all evaluated in clinic at 1 year.

#### Short-Term Results: 0 to 3 Months (Masked Period)

A baseline comparison of dextrose and control groups per joint (Table 1) revealed that the dextrose group had fewer female

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dextrose (n=30)</th>
<th>Control (n=24)</th>
<th>$P$ value$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: female</td>
<td>22 (73)</td>
<td>23 (96)</td>
<td>.03</td>
</tr>
<tr>
<td>Age (y)</td>
<td>44±14.1</td>
<td>50±13.4</td>
<td>.15</td>
</tr>
<tr>
<td>Pain duration (y)</td>
<td>9.5±9.8</td>
<td>17.9±13.2</td>
<td>.01</td>
</tr>
<tr>
<td>Pain score (on a 0-10 NRS)</td>
<td>7.8±1.2</td>
<td>8.2±1.2</td>
<td>.22</td>
</tr>
<tr>
<td>Jaw dysfunction score (on a 0-10 NRS)</td>
<td>7.1±1.1</td>
<td>6.7±0.9</td>
<td>.10</td>
</tr>
<tr>
<td>Maximal incisor opening (mm)</td>
<td>43.4±5.7</td>
<td>39.0±6.8</td>
<td>.01</td>
</tr>
<tr>
<td>RDC/TMD I-myofascial$^d$</td>
<td>23 (77)</td>
<td>18 (75)</td>
<td>.89</td>
</tr>
<tr>
<td>RDC/TMD II-disc displacement$^d$</td>
<td>13 (43)</td>
<td>9 (38)</td>
<td>.67</td>
</tr>
<tr>
<td>RDC/TMD version III-other joint condition$^d$</td>
<td>17 (57)</td>
<td>11 (46)</td>
<td>.43</td>
</tr>
</tbody>
</table>

$^a$NRS = Numerical Rating Scale; RDC/TMD = Research Diagnostic Criteria for Temporomandibular Dysfunction.  
$^b$Data are mean ± SD or No. (percentage).  
$^c$Intragroup statistical comparison using $t$ tests for numerical variables and Pearson $\chi^2$ tests for categorical variables.  
$^d$Percentage does not sum to 100, as joints may be assigned to >1 RDC/TMD category.
participants (22 of 30 [73%] vs 23 of 24 [96%]; P = .03), a shorter pain duration (9.5 ± 9.8 years vs 17.9 ± 13.2 years; P = .01), and a larger MIO (43.4 ± 5.7 mm vs 39.0 ± 6.8 mm; P = .01). Joints were treated in participants with a mean age of 46 ± 14 years and moderate to severe pain (8.0 ± 1.2) and dysfunction (6.9 ± 1.0). RDC/TMD group assignments were distributed as myofascial (41 [76%]), disc dysfunctions (22 [41%]), and other joint conditions (28 [52%]). From 0 to 3 months, dextrose- and control-treated participants received 2.8 ± 0.6 and 3.0 ± 0.0 injections, respectively. From 3 to 12 months, after crossover of control-treated participants to active dextrose injection, jaws initially treated with dextrose received 2.7 ± 2.0 additional injections of dextrose and those initially treated with control injection received 4.0 ± 2.1 dextrose injections.

The results of the analysis of outcomes at baseline and 3-month follow-up are reported in Table 2, including sex, pain duration, and baseline MIO as covariates. The change in NRS pain and dysfunction scores was greater for the dextrose group than for the control injection group: pain, 4.3 ± 2.9 points vs 1.8 ± 2.7 points (P = .02); and dysfunction, 3.5 ± 2.8 points vs 1.0 ± 2.1 points (P = .008), respectively. Maximal interincisal opening improvement (increase) from 0 to 3 months for dextrose and control groups was 1.5 ± 4.1 mm vs −1.8 ± 5.1 mm (P = .006), respectively. The percentage of joints with 50% or more improvement in pain at 3 months was 47% (14 of 30) in the dextrose group and 21% (5 of 24) in the control group (P = .04). The percentage of joints with 50% or more improvement in dysfunction at 3 months was 60% (18 of 30) in the dextrose group and 13% (3 of 23) in the control group (P = .001). Participant satisfaction, on a 1 to 5 scale, at 3 months was 3.6 ± 1.7 points for the dextrose group and 2.3 ± 1.4 points for the control group (P = .02).

Long-Term Results: 0 to 12 Months (Including Open-Label Treatment From 3 to 12 Months)

An analysis of change scores through 12 months revealed that in participants receiving dextrose in months 0 to 3, jaw pain and jaw dysfunction continued to improve compared with baseline and 3-month status (Table 2).
In initial control group participants who switched over to receive dextrose injections from months 3 to 12, jaw pain, jaw dysfunction, and MIO improvements statistically matched those of the initial active group at month 12 (Table 2 and Figure 4). Pooled data analysis revealed that 50% or more improvement in pain and dysfunction was achieved by 38 of 54 (70%) and 39 of 54 (72%) of jaws, respectively, at 12 months. The mean improvement at 12 months, from baseline, was as follows: jaw pain, 5.2/2.7 points (66%); jaw dysfunction, 4.1/2.8 points (59%); and MIO, 2.1/5.5 mm.

Analysis of Outcomes per RDC/TMD Subgroups During Masked and Open-Label Periods

A comparison of demographic characteristics according to RDC/TMD group classification (Table 3) revealed no significant baseline differences between RDC/TMD diagnostic groups.

Despite limited numbers in individual RDC/TMD groups, in the 3-month masked period dextrose injection outperformed control injection in the 2 largest groups. The myofascial group improved more in pain ($P=.008$) and dysfunction ($P=.01$), and the other joint diagnosis group improved more in dysfunction ($P=.007$) and MIO ($P=.002$) (Table 4).

After the open-label period (Table 4), there were no significant differences between jaws treated with dextrose originally and jaws treated with control injection, followed by dextrose from 3 to 12 months, regardless of the RDC/TMD group. As shown in Figure 5, improvement in jaw pain, jaw dysfunction and MIO from 0 to 12 months was similar for all 3 RDC/TMD diagnostic groups, with no significant between-group multivariate difference at the 12-month follow-up (myofascial [P=.18], disc dysfunction [P=.92], other joint dysfunction [P=.38]).

Effect on Joints With Initial Restriction in Mouth Opening

Table 5 lists the change in MIO for jaws with an initial opening restriction (MIO <40 mm) and those without an initial opening restriction (MIO ≥40 mm). Greater improvement in MIO was obtained in the dextrose group than in the control injection group during the 3-month masked treatment period (6.2±6.0 mm vs −0.4±4.3 mm, respectively; $P=.01$). At the 12-month time point, there was no difference in MIO improvement between jaws with and without an initial restriction.
TABLE 3. Baseline Participant Characteristics by RDC/TMD Classification

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Myofascial (n=41)</th>
<th>Disc dysfunction (n = 22)</th>
<th>Other joint condition (n=23)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex; female</td>
<td>33 (81)</td>
<td>20 (91)</td>
<td>23 (82)</td>
<td>.56</td>
</tr>
<tr>
<td>Age (y)</td>
<td>47.5±14.9</td>
<td>46.6±15.7</td>
<td>45.5±14.8</td>
<td>.86</td>
</tr>
<tr>
<td>Pain duration (y)</td>
<td>13.9±13.0</td>
<td>11.1±11.6</td>
<td>12.4±12.1</td>
<td>.68</td>
</tr>
<tr>
<td>Pain score (on a 0-10 NRS)</td>
<td>8.0±1.1</td>
<td>8.2±1.1</td>
<td>8.0±1.5</td>
<td>.81</td>
</tr>
<tr>
<td>Jaw dysfunction score (on a 0-10 NRS)</td>
<td>7.0±1.0</td>
<td>7.1±1.0</td>
<td>6.8±1.0</td>
<td>.63</td>
</tr>
<tr>
<td>MIO (mm)</td>
<td>41.5±6.6</td>
<td>40.7±7.0</td>
<td>40.4±5.6</td>
<td>.76</td>
</tr>
</tbody>
</table>

MIO = maximal interincisal opening; NRS = Numerical Rating Scale; RDC/TMD = Research Diagnostic Criteria for Temporomandibular Dysfunction. Data are mean ± SD or No. (percentage). Intrigroup statistical comparison using t tests for numerical variables and Pearson χ² tests for categorical variables.

opening restriction (6.5±4.8 vs 6.8±6.3, respectively; P=.33).

DISCUSSION

This randomized controlled trial (RCT) with crossover of control group participants to active therapy found that intra-articular dextrose injection (prolotherapy) substantially outperformed control injection in self-reported pain and dysfunction improvement and mouth opening in comparison to control injection at 3-month follow-up. Upon crossing over to dextrose solution, improvements in the initial control group approximated those of the initial dextrose-receiving group at 12 months and 70% of participants reported at least 50% improvement in jaw pain and dysfunction. Participants in all 3 RDC/TMD diagnostic groups responded with similar clinically significant improvements in pain and function to 12 months. In addition, participants whose mouth opening was initially restricted gained significant mouth opening ability. The direction and scale of these results are generally consistent with those of other reports of DPT for TMD and other musculoskeletal pain conditions.11,20

One retrospective case series,21 3 prospective case series,14,22,23 and 2 RCTs12,24 have reported favorable clinical outcomes of DPT for TMD, measured as a marked subjective reduction in episodes of painful subluxation. However, only 1 prospective case series and 1 RCT used a quantifiable pain measure (visual analog scale or NRS) as well as a measure of MIO (in millimeters), pre- and posttreatment.14,24 Refai,14 in the largest prospective study to date (n=61), reported a 91% mean improvement in TMJ pain in consecutive patients treated with dextrose injection, whereas Kilic and Gungormus24 reported pain improvement with the use of either saline (69%) or dextrose (79%) injection without a between-group difference. The latter study may have been underpowered; only 15 participants were in each group, and there was a 20% dropout from the saline arm. In addition, participants received needleling in 5 locations on 3 occasions and multiple injections with bony contact; such injections, regardless of the injectate, are active therapy.25,26

Previous studies included extra-articular injection in an effort to reduce pain and subluxation. Refai14 and Kilic and Gungormus24 reported mean MIO reductions of 2.5 and 3.8 mm, respectively, as a result of treatment. However, pre- and posttreatment open mouth tomographic views revealed that a reduction in MIO was not accompanied by a reduction in actual subluxation, despite marked pain reduction during subluxation.14 Whether, or how, reduced MIO may be related to pain diminution in these studies is unclear.

The present study used a simplified injection protocol that can be easily taught and learned as well as avoids cortical and
### TABLE 4. Change Scores for Pain, Dysfunction, and Mouth Opening According to the RDC/TMD Diagnostic Group

<table>
<thead>
<tr>
<th>RDC-TMD group</th>
<th>Treatment group</th>
<th>Mean ± SD at 0-3 mo</th>
<th>n at 0-3 mo</th>
<th>P value at 0-3 mo</th>
<th>Between-group Mean ± SD at 0-12 mo</th>
<th>n at 0-12 mo</th>
<th>P value at 0-12 mo</th>
<th>Within-group Mean ± SD at 0-3 mo</th>
<th>n at 0-3 mo</th>
<th>P value at 0-3 mo</th>
<th>Between-group Mean ± SD at 0-12 mo</th>
<th>n at 0-12 mo</th>
<th>P value at 0-12 mo</th>
</tr>
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<tbody>
<tr>
<td>Change in pain score (on a 0-10 NRS)</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Myofascial</td>
<td>Dextrose</td>
<td>4.7 ± 3.1</td>
<td>23</td>
<td>.008</td>
<td>.21</td>
<td>4.8 ± 3.1</td>
<td>23</td>
<td>.52</td>
<td>32</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Control</td>
<td>2.1 ± 2.9</td>
<td>18</td>
<td></td>
<td></td>
<td>5.3 ± 2.5</td>
<td></td>
<td></td>
<td>18</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nonmyofascial</td>
<td>Dextrose</td>
<td>3.1 ± 1.5</td>
<td>7</td>
<td>.07</td>
<td></td>
<td>6.0 ± 2.6</td>
<td>7</td>
<td>.68</td>
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<tr>
<td></td>
<td>Control</td>
<td>1.0 ± 2.2</td>
<td>6</td>
<td></td>
<td></td>
<td>5.4 ± 2.3</td>
<td></td>
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<tr>
<td>Discal dysfunction</td>
<td>Dextrose</td>
<td>4.9 ± 3.0</td>
<td>13</td>
<td>0.13</td>
<td>.18</td>
<td>5.3 ± 3.0</td>
<td>13</td>
<td>0.76</td>
<td>.65</td>
<td></td>
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<tr>
<td></td>
<td>Control</td>
<td>2.8 ± 3.2</td>
<td>9</td>
<td></td>
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<td>5.7 ± 2.9</td>
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<td></td>
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<tr>
<td>Non-discal dysfunction</td>
<td>Dextrose</td>
<td>3.9 ± 2.7</td>
<td>17</td>
<td>.06</td>
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<td>4.9 ± 3.0</td>
<td>17</td>
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<td></td>
<td>Control</td>
<td>1.2 ± 2.3</td>
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<td>5.2 ± 2.1</td>
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<tr>
<td>Other joint condition</td>
<td>Dextrose</td>
<td>3.6 ± 2.7</td>
<td>17</td>
<td>0.14</td>
<td>.98</td>
<td>4.5 ± 3.1</td>
<td>17</td>
<td>0.25</td>
<td>.46</td>
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<tr>
<td></td>
<td>Control</td>
<td>2.0 ± 2.5</td>
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<td>5.8 ± 2.4</td>
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<td>Non-other joint condition</td>
<td>Dextrose</td>
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<td>5.7 ± 2.8</td>
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<tr>
<td></td>
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<td>1.6 ± 2.9</td>
<td>13</td>
<td></td>
<td></td>
<td>5.0 ± 2.3</td>
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<td>Change in dysfunction score (on a 0-10 NRS)</td>
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<tr>
<td>Myofascial</td>
<td>Dextrose</td>
<td>3.7 ± 3.1</td>
<td>23</td>
<td>.01</td>
<td>.52</td>
<td>4.0 ± 3.2</td>
<td>23</td>
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<tr>
<td></td>
<td>Control</td>
<td>1.3 ± 2.2</td>
<td>18</td>
<td></td>
<td></td>
<td>3.9 ± 2.8</td>
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<tr>
<td>Nonmyofascial</td>
<td>Dextrose</td>
<td>3.0 ± 1.3</td>
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<td>4.9 ± 1.5</td>
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<td>.75</td>
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<td>3.4 ± 2.9</td>
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<td></td>
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<tr>
<td>Myofascial</td>
<td>Dextrose</td>
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<td>23</td>
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<td>−0.8 ± 4.7</td>
<td>18</td>
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<td>2.2 ± 5.3</td>
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<tr>
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<td>4.0 ± 5.0</td>
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<td>6</td>
<td></td>
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<td>5.7 ± 8.5</td>
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<td>Discal dysfunction</td>
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<td>1.1 ± 2.7</td>
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<td>.85</td>
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<td>Non-discal dysfunction</td>
<td>Dextrose</td>
<td>1.9 ± 5.0</td>
<td>17</td>
<td>.023</td>
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<td>1.7 ± 5.1</td>
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<td>−2.1 ± 4.5</td>
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<td>2.5 ± 6.4</td>
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<td>Other joint condition</td>
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<td>2.3 ± 4.7</td>
<td>17</td>
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<td>.45</td>
<td>2.2 ± 4.9</td>
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<td></td>
<td>Control</td>
<td>−3.6 ± 4.4</td>
<td>11</td>
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<td>3.5 ± 7.3</td>
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<td>Non-other joint condition</td>
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<tr>
<td></td>
<td>Control</td>
<td>−0.2 ± 5.3</td>
<td>13</td>
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<td>2.8 ± 0.3</td>
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</table>

*RDC/TMD = Research Diagnostic Criteria for Temporomandibular Dysfunction.

Control group received dextrose during the open-label period of 3-12 mo.
capsular contact, minimizing potential active-treatment effects of needling. Therefore, the protocol is a relatively pure test of the specific effects of dextrose.

The mechanism of action of hypertonic dextrose is unclear; studies suggest a multifactorial effect. Animal research suggests that hypertonic dextrose injection initiates fibroblast proliferation, with production of stronger, thicker, and organized connective tissue.\textsuperscript{27,28} Pericapsular fibrosis, after pericapsular injection around the TMJ, has been suggested by pre- and post-treatment magnetic resonance imaging data.\textsuperscript{23} Although proliferation is potentially helpful in conditions associated with degenerative extra- and intra-articular tissues, it may not be the primary mechanism of change in the present study. We selected an intra-articular protocol to avoid such potential effects, which could further limit the range of motion associated with mouth opening. The potential proliferative effects of dextrose and extra-articular needling may not always be clinically beneficial. Dextrose injection at the carpal tunnel offers a useful example.

Ten percent dextrose injected into subsynovial tissue about the flexor digitorum tendons induced proliferation of subsynovial tissue, causing secondary compression of the median nerve and induction of carpal tunnel syndrome in a rabbit model.\textsuperscript{27-30} In contrast, injection in the carpal tunnel using 5% dextrose, and avoiding direct injection into subsynovial tissue, has been reported as clinically beneficial in human carpal tunnel syndrome, and reduction in median nerve swelling was found by pre- and posttreatment high-resolution interval ultrasonography.\textsuperscript{31,32}

In studies that include intra-articular dextrose injections in participants with knee osteoarthritis, dextrose is implicated as an independent agent in pain diminution.\textsuperscript{33,34} Postprocedure arthroscopic evaluation further suggests a chondrogenic effect of dextrose.\textsuperscript{35} Whether similar effects are present in the present study are not known.

A therapeutic benefit of dextrose based on a neurogenic mechanism was proposed in 2008\textsuperscript{36} and is supported by recent RCTs and open-label studies using dextrose.

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**FIGURE 5.** Numerical Rating Scale (0-10) change scores for jaw pain and jaw dysfunction according to the Research Diagnostic Criteria for Temporomandibular Dysfunction diagnostic group assignment. \textsuperscript{a}Control group received dextrose injections, as requested, after 3 months, during the open-label period of the study.
hydrodissection for carpal tunnel syndrome, peritendinous dextrose injection for Achilles tendinopathy, and epidural dextrose for chronic low back pain. Similar effects have been reported in a retrospective analysis of the results from regional hydrodissection using dextrose in patients with various neurogenic pain conditions of the upper body.

Several neural mechanisms have been hypothesized. First, downregulation of the transient receptor potential vanilloid receptor 1 ion channel is a primary therapeutic target in chronic pain management. A class effect of sugars resulting in indirect downregulation of the effects of transient receptor potential vanilloid receptor 1 ion channel activation has been proposed on the basis of an RCT using a polyol (mannitol) with structural similarity to dextrose. Second, in vitro nociceptive C fibers in corneal explants fire faster in the presence of hypoglycemia, followed by a prompt reduction in firing rate with correction of the hypoglycemic state. This suggests that a relative hypoglycemia of high-energy cells (nerves) may hypopolarize pain-producing C fibers, lowering the threshold required for depolarization and resultant pain perception. Third, coadministration of 5% dextrose to reduce pain upon infusion of pain-inducing chemotherapeutic agents or microspheres may point to a hyperpolarization effect of dextrose on the cell membrane of pain-producing C fibers, increasing the threshold required for depolarization. Although interesting and consistent with clinical studies, none of these theories has been directly tested in a prolotherapy-specific model.

Limitations of this study include a relatively small sample size. However, the sample size was adequate to detect between-group differences. A larger study is required to further determine whether all RDC/TMD categories respond similarly to intra-articular dextrose. Randomization produced 2 groups that were not completely similar. We cannot exclude the possibility of a randomization bias favoring the active group. However, the mean pain duration was more than 8 years for each group, each group improved similarly in the long term after receiving dextrose, and covariate analysis indicated no significant effect of pain duration, initial MIO, or sex on between-group analysis of change in pain, dysfunction, or MIO. Finally, the use of change scores mitigates the effect of between-group differences. Blinding was not assessed, possibly introducing bias; however, procedures to optimize random allocation and blinding were clearly described and followed, both solutions are colorless and transparent, and contact with gloves was minimized to avoid any awareness of a slight difference in solution viscosity.

### TABLE 5. Improvement in MID During Masked (0-3) and Open-Label (3-12) Month Periods for Joints With an Initial MID of <40 mm and an Initial MID of ≥40 mm

<table>
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<tr>
<th>Group</th>
<th>Treatment</th>
<th>Change in jaw opening from baseline</th>
</tr>
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<tr>
<td></td>
<td></td>
<td>0-3 mo</td>
</tr>
<tr>
<td>MID &lt;40 mm</td>
<td>Dextrose (n=6)</td>
<td>6.2±6.0</td>
</tr>
<tr>
<td></td>
<td>Control (n=12)</td>
<td>−0.4±4.3</td>
</tr>
<tr>
<td></td>
<td>Combined (n=18)</td>
<td>NA</td>
</tr>
<tr>
<td>MID ≥40 mm</td>
<td>Dextrose (n=24)</td>
<td>0.4±2.5</td>
</tr>
<tr>
<td></td>
<td>Control (n=12)</td>
<td>−3.1±5.7</td>
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<tr>
<td></td>
<td>Combined (n=32)</td>
<td>NA</td>
</tr>
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</table>

*MID = maximal interincisal distance.

*Data are mean ± SD.

*Control group received dextrose during the open-label period of 3-12 mo.

*Dextrose injection significantly outperformed control injection in mouth opening improvement from 0 to 3 mo (P=.01).

*Significant difference in mouth opening from 0 to 12 mo for those with an initial mouth opening restriction (P<.001).
Strengths of this study include excellent participant retention and data capture as well as treatment of an often refractory condition using a simple low-cost approach that is satisfying to participants.

CONCLUSION
In study participants with TMD, intra-articular DPT was superior to lidocaine injections and may be appropriate care for patients who have failed more conservative measures. The technique is straightforward to learn, takes less than 1 minute to perform, and is inexpensive and satisfactory to patients.

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Abbreviations and Acronyms. DPT = dextrose prolotherapy; MIO = maximal interincisal opening; NRS = Numerical Rating Scale; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial; RDC/TMD = Research Diagnostic Criteria for Temporomandibular Dysfunction; TMD = temporomandibular dysfunction; TMJ = temporomandibular joint

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Potential Competing Interests: Dr Cheng received $610 as a consultant for power analysis and preliminary data evaluation related to this study prior to accepting an invitation to co-author this study. Dr Rabago is President of the Hackett Hemwall Patterson Foundation, a nonprofit (501c3) organization that teaches and provides prolotherapy to medical providers and needy patients, respectively. The other authors report no competing interests.

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REFERENCES
alternatives to the American College of Rheumatology 20.
19. Rauch A, Schierz O. Reliability of mandibular movement assess-
A systematic review of dextrose prolotherapy for chronic
musculoskeletal pain. Clin Med Insights Arthritis Musculoskelet
Disord. 2016;9:139-159.
prolotherapy in the management of temporomandibular joint
22. Zhou H, Hu K, Ding Y. Modified dextrose prolotherapy for
recurrent temporomandibular joint dislocation. Br J Oral Max-
23. Majumdar SK, Krishna S, Chatterjee A, Chakrabarty R, Ansari N. Single injection technique prolotherapy for hypermo-
tility disorders of TMJ using 25% dextrose: a clinical study.
24. Cömert Kilic S, Gungörmüş M. Is dextrose prolotherapy supe-
rior to placebo for the treatment of temporomandibular joint
hypermobility? A randomized clinical trial. Int J Oral Maxillo-
Dextrose prolotherapy versus control injections in painful rota-
tor cuff tendinopathy. J Orthop Res. 2016;34(1):9-16; discus-
sion 16.
26. Yoshi Y, Zhao C, Schmelzer JD, Low PA, An KN, Amadio PC.
Effects of multiple injections of hypertonic dextrose in the rab-
it rabbit carpal tunnel: a potential model of carpal tunnel syndrome
27. Oh S, Ettema AM, Zhao C, et al. Dextrose-induced submyo-
nar connective tissue fibrosis in the rabbit carpal tunnel model: a
potential model to study carpal tunnel syndrome. Hand (N Y).
28. Yoshi Y, Zhao C, Schmelzer JD, Low PA, An KN, Amadio PC.
The effects of hypertonic dextrose injection on connective tis-
ue and nerve conduction through the rabbit carpal tunnel. Arch
29. Yoshi Y, Zhao C, Schmelzer JD, Low PA, An KN, Amadio PC.
Effects of hypertonic dextrose injections in the rabbit carpal
30. Wu YT, Ho TY, Chau YC, et al. Six-month efficacy of perineu-
ral dextrose for carpal tunnel syndrome: a prospective, ran-
31. Mauermann ML, Watson JC. A novel treatment for carpal tun-
32. Rabago D, Patterson JJ, Mwindi M, et al. Dextrose prolotherapy
for knee osteoarthritis: a randomized controlled trial [published
correction appears in Fam Med. 2013;45(1):480]. Ann Fam
tween disease-specific quality-of-life and magnetic reso-
nance imaging outcomes in a clinical trial of prolotherapy
94(11):2075-2082.
34. Topol GA, Podesta LA, Reeves KD, et al. The chondrogenic ef-
ficacy of intra-articular hypertonic-dextrose (prolotherapy) in se-
35. Lyfogt J. Pain conundrums: which hypothesis? Central nervous
system sensitization versus peripheral nervous system auton-
36. Yelland MJ, Sweeting KR, Lyfogt JA, Ng SK, Scuffham PA, Evans KA. Prolotherapy injections and eccentric loading exer-
cises for painful Achilles tendinosis: a randomised trial. Br J
37. Maniquis-Smigel L, Dean Reeves K, Jeffrey Rosen H, et al. Short
term analgesic effects of 5% dextrose epidural injection for
chronic low back pain: a randomized controlled trial. Anesth
and potential cumulative benefit from caudal epidural D5W in
consecutive participants with chronic low back and buttock/leg
pain [published online ahead of print June 8, 2018]. J Altern
39. Lam SHY, Reeves KD, Cheng AL. Transition from deep regional
blocks toward deep nerve hydrodissection in the upper body
and torso: method description and results from a retrospective
chart review of the analgesic effect of 5% dextrose water as the
primary hydrodissection injectate. Biomed Res Int. 2017;2017:
7920438.
40. Malek N, Piják A, Kołosowska N, Kucharczyk M, Starowicz K.
The importance of TRPV1-sensitisation factors for the develop-
41. Bertrand H, Kryszcz M, Reeves KD, Lyfogt J, Rabago D. Topical
mannitol reduces capsaicin-induced pain: results of a pilot level,
double-blind randomized controlled trial. PM R. 2015;7(11):
1111-1117.
42. Mawer MB, Tanrellian DL. Activation of C fibers by metabolic
perturbations associated with tourniquet ischemia. Anesthesia-
43. Hosokawa A, Nakashima T, Ogawa Y, Kazawa K, Kiba T. Coad-
mistration of 5% glucose solution relieves vascular pain in the
patients administered gemcitabine immediately. J Oncol Pharm
5% glucose solution has a decrease in bendamustine-
45. Paprottka KJ, Lehner A, Fendler WP, et al. Reduced periproce-
dural analgesia after replacement of water for injection with
glucose 5% solution as the infusion medium for 90Y-Resin mi-