Effect of Local Anesthetic Versus Botulinum Toxin-A Injections for Myofascial Pain Disorders

A Systematic Review and Meta-Analysis

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Objective: Myofascial pain is a chronic pain disorder characterized by the presence of painful localized regions of stiff muscle and/or myofascial trigger points. Intramuscular myofascial trigger point injections are considered first-line treatments for myofascial pain. Common injectates include local anesthetics and botulinum toxin-A (BTX-A). The objective of this systematic review was to compare the effectiveness of local anesthetics and BTX-A on pain intensity in patients with myofascial pain.

Methods: A comprehensive systematic search of 3 databases, EMBASE, CENTRAL, and Medline was conducted. The search was comprised of words to describe "myofascial pain" and "injections." We performed a meta-analysis comparing local anesthetic and BTX-A injections across these follow-up week periods: 0 (immediately following the injection), 1 to 2, 3 to 4, 5 to 6, 7 to 8, 9 to 10, 11 to 12, 16, 18, 24 weeks with local anesthetics and BTX-A as subgroups. We also performed subgroup analyses comparing the effectiveness of local anesthetic injections and BTX-A injections at various muscle locations and comparing the effectives of single versus multiple injection sessions.

Results: In total, 33 studies were included. A qualitative analysis suggested that local anesthetics and BTX-A were inconsistently effective at mitigating pain across all follow-up periods. The meta-analyses revealed that local anesthetic injections were more effective than BTX-A at mitigating pain intensity. Multiple injection sessions of local anesthetics were more beneficial than a single session.

Conclusions: Additional studies are needed to determine sources of heterogeneity mediating the observed differences in effectiveness of local anesthetic and BTX-A injections among the studies. Additional replicative studies are also needed to delineate the relative efficacy and effectiveness of local anesthetic and BTX-A injection. The quantitative results of this study suggest that patients overall experience more pain relief with local anesthetic injections.

Key Words: myofascial pain, trigger points, botulinum toxin-A, injectates, local anesthetics

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BACKGROUND AND RATIONALE

Myofascial pain is a chronic pain disorder prevalent in ~30% of general clinics and 85% of pain clinics, affecting a wide range of patient populations including individuals with regional pain, fibromyalgia, cancer, and inflammatory disorders.[1–5] Myofascial pain is characterized by the presence of painful localized regions of muscle and/or myofascial trigger points (MTrP). MTrPs are localized contractures of skeletal muscle that are stiff, tender, and hypersensitive on palpation.[6] Poor vascular flow and an inflammatory milieu is found at the region of the trigger point.[7,8] It is postulated that the formation of MTrPs is initiated by taut band formation (regions of painful tight muscle).[9] This can be induced by muscle overexertion, direct trauma, and/or repeated muscle contractures that reduce adenosine triphosphate and oxygen supplies as and increase intramuscular calcium levels, effectively causing an energy crisis and hindering the muscle's relaxation.[9,10] The integrated hypothesis suggests that excessive acetylcholine release from motor endplates and receptor potentiation from low pH environments resulting from poor vascular flow results in the formation of MTrPs and contributes to the maintenance of the muscle's contractile state.[7,11,12] It is also thought that MTrPs are maintained through a spinal feedback mechanism, whereby dorsal horn segments are sensitized by afferent nociceptive input from the abnormal contracture. This in turn creates central plastic changes that sensitize active and dormant efferent nociceptive nerves, which then release inflammatory discharge onto the region of the MTrP and incur pain.[13–17]

Intramuscular injections are considered the first-line treatments for myofascial pain.[18] Injectates include local anesthetics and botulinum toxin-A (BTX-A), which act to inhibit aspects of the aforementioned mechanisms. Local anesthetics inhibit efferent and afferent nerve signals within the region of the MTrP, reducing pain and disrupting the spinal facilitation mechanism maintaining the MTrP. BTX-A inhibits acetylcholine activity which promotes muscle relaxation, and theoretically the MTrP contracture.[18] Previous studies assessing the effectiveness of local anesthetic and BTX-A injections

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report heterogenous results.[19–21] Some studies suggest that local anesthetic and BTX-A injections are equally beneficial relative to saline control injections, whereas others report significant improvements in reported pain relative to controls following local anesthetic or BTX-A injections.[19–21] There are no current reviews, to our knowledge and according to a systematic search, assessing the relative benefits of local anesthetic and BTX-A injections on myofascial pain. Reviews assessing the efficacy of injection therapy on low back pain have found no results for the benefit of corticosteroid and local anesthetic injections. A review by Ho and Tan[22] found only 5 trials assessing the effect of BTX-A on myofascial pain with 4 trials concluding BTX-A was ineffective. As these injectates are commonly used clinically, there is a need for robust data to inform the effectiveness of injection treatments and their clinical utility for myofascial pain.

OBJECTIVES

The objective of this systematic review was to compare the effectiveness of local anesthetics and BTX-A on reported pain in patients with myofascial pain by: (1) assessing the effects of local anesthetics and BTX-A on reported pain over several follow-up periods; (2) assessing the effects of single and multiple injection sessions of each injectate type on changes in reported pain; and (3) to determine whether reported pain differs based on the region of injection for each type of injectate. This study is exploratory, therefore the authors present no hypotheses.

METHODS

This review was completed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[23]

Search Strategy

An information specialist conducted a comprehensive systematic search of 3 databases, EMBASE, Cochrane CENTRAL, and Medline. The search was comprised of keywords and patients headings to describe the following key terms: "myofascial pain," "injections" as well as the various injectate fluids such as local anesthetics, hyaluronidase, and BTX-A, and "Clinical trials." The search was limited to English studies and excluded animal studies. The search in each database was conducted from the inception of the database until May 2017. The Medline search strategy can be found in Appendix A (Supplemental Digital Content 1, http://links.lww.com/CJP/A553).

Eligibility Criteria

Inclusion Criteria

Study types
- Randomized controlled trials
- Controlled trials
- Randomized trials

Participants
- Patient populations with myofascial pain disorders confirmed by expert assessment (whiplash associated disorder, mechanical neck disorder, myofascial pain syndrome)

Types of interventions
- Local anesthetic injections into painful hypertonic muscle and/or an MTrP
- BTX-A injections into painful hypertonic muscle and/or an MTrP

Comparison
- Placebo interventions
- Alternate interventions (eg, needling, acupuncture, massage)

Exclusion Criteria

Study types
- Other study designs including cohort, case series, case studies
- Studies with nonparametric reporting of outcome measures
- ABSTRACTs

Participants
- Pediatric populations
- Animal populations

Types of interventions
- Injection mixtures

Outcome Measures

Patient-reported pain including but not limited to the visual analog scale (VAS) and the Neck Pain and Disability Scale (NPAD) will be the outcome measure of this study. The VAS measures subjective pain on a scale of 0 to 10, 0 representing no pain and 10 representing the most severe pain.[24] The NPAD assesses neck pain using a 20-item questionnaire with responses scaled from 0 to 5 for a total possible score of 100.[25]

Risk of Bias

Risk of bias was determined using the criteria set by the Cochrane Handbook of Systematic Reviews by the Cochrane collaboration.[26] The following risk of bias parameters were assessed:
- Selection: random sequence generation
- Performance: allocation concealment
- Blinding: blinding of personnel and participants
- Measurement: blinding of outcome assessment
- Attrition: incomplete outcome data
- Reporting: selective reporting

These 6 items assessed were given a rating of low risk of bias, unclear risk of bias, and high risk of bias. If the study explicitly stated their method for addressing a parameter associated with the bias, then the parameter was deemed low risk or high risk accordingly. If the article did not state how they addressed a bias, then the risk was recorded as unclear.

Reviewing Procedures

Reviewers S.A. and S.S. screened the titles and abstracts of the resultant papers for their inclusion or exclusion based on eligibility criteria described above. Reviewer S.K. resolved conflicts for article inclusion. Patient-reported pain outcomes were extracted from each of the included studies at all after injection measurement times provided in the studies. If values were not reported but graphical representations were available, the values of interest were extracted using standardized measurement tools. Figure 1 presents a PRISMA diagram outlining the process of article selection. Reviewers S.A. and S.S. determined the risk of bias in the included studies. Differences in ratings were resolved by agreement.

The included studies were assessed qualitatively for the sample size, sex breakdown of the study sample, mean age of the study sample, study experimental and control interventions, region of injection, outcome measures used, the quantity or concentration of the used injectate, the number of treatment sessions given to participants, and the statistical improvement of

the experimental intervention relative to the control as determined by the study authors at all reported follow-up periods. Trends in the study results were reported.

Statistical Analysis

We performed a meta-analysis of all injectate data with follow-up period and type of injectate (local anesthetic vs. BTX-A) as concurrent subgroups. The follow-up periods included in the analysis were as follows: 0, 1 to 2, 3 to 4, 5 to 6, 7 to 8, 9 to 10, 11 to 12, 16, 18, and 24 weeks. If a study had multiple comparisons, these were included as separate entries in the analysis. Separate subgroup analyses were performed on the effect of one compared with multiple sessions of local anesthetic or BTX-A trigger point injections, and on the effect of local anesthetic or BTX-A injections at different body regions. If a study injected 2 different body regions, the study data were included in both subgroup analyses. Standardized mean differences (SMD) for the effects of injection (local anesthetic and BTX-A) interventions were computed using Revman version 5.3 (Revman software, Cochrane Collaboration). A random effects model (DerSimonian and Laird method[27]) was used when pooling findings given the heterogeneity in injectates among the studies (eg, bupivacaine, lidocaine, prilocain). The 95% confidence intervals were computed for each SMD. The Cohen criteria were used to determine the effect size of the computed SMD values. An SMD value of 0.2 to 0.5 was considered small, an SMD of 0.5 to 0.8 was considered moderate, and an SMD > 0.8 was deemed large based on the Cohen criteria.[28] SMDs < 0.2 were considered unsubstantial.

I^2 values were computed and the χ^2 ($\alpha = 0.05$) test was performed to assess for heterogeneity. I^2 cutoffs for heterogeneity provided by the Cochrane Handbook for Conducting Systematic Reviews were used to determine the extent of heterogeneity among studies within the analyses. The following ranges are the outlined cutoffs: $I^2 < 25\%$ is low, I^2 between 25% and 50% is moderate, and an I^2 over 50% is high. Publication bias was assessed using the Egger test.[29]

RESULTS

The PRISMA guidelines for article screening were followed (Fig. 1). After the removal of duplicates, 2288 articles remained for the initial screening. After full screening, 33 articles met the eligibility criteria for the review. One study assessed the effect of both lidocaine and BTX-A trigger point injections.[30] A total of

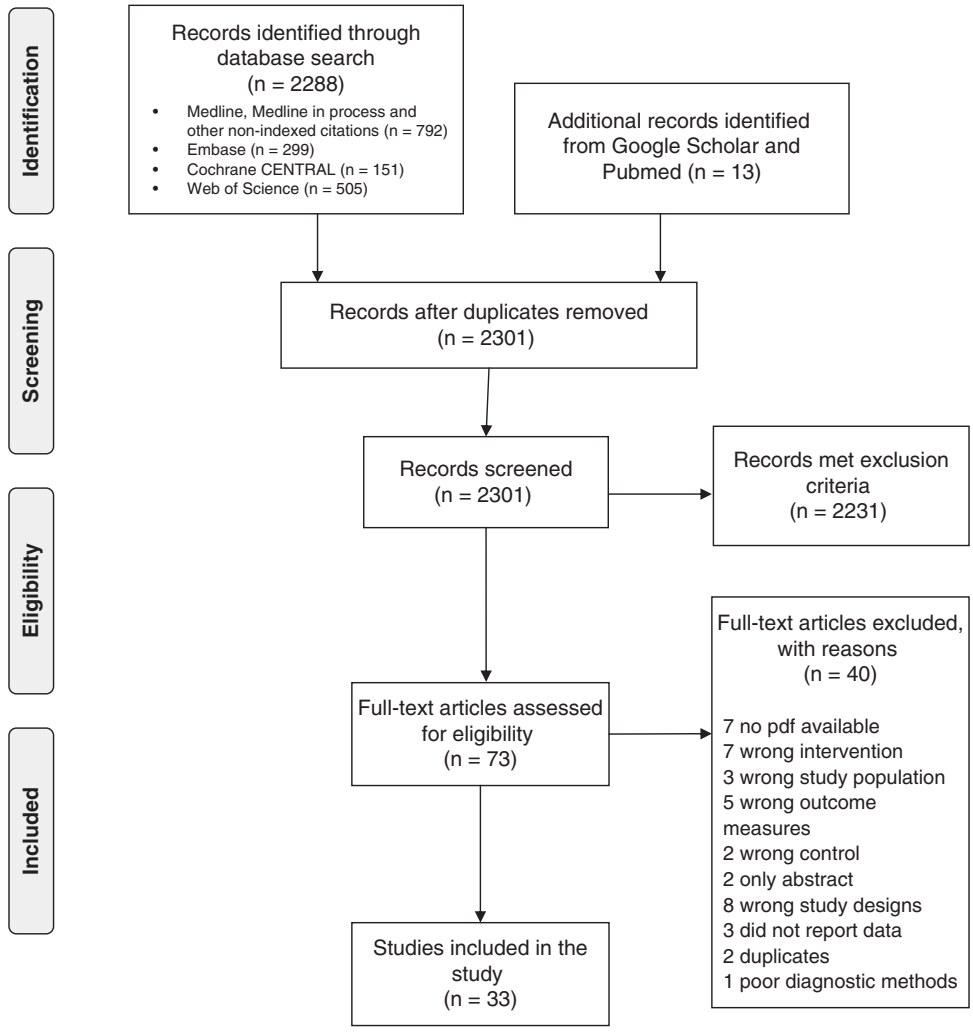

FIGURE 1. PRISMA flow diagram.

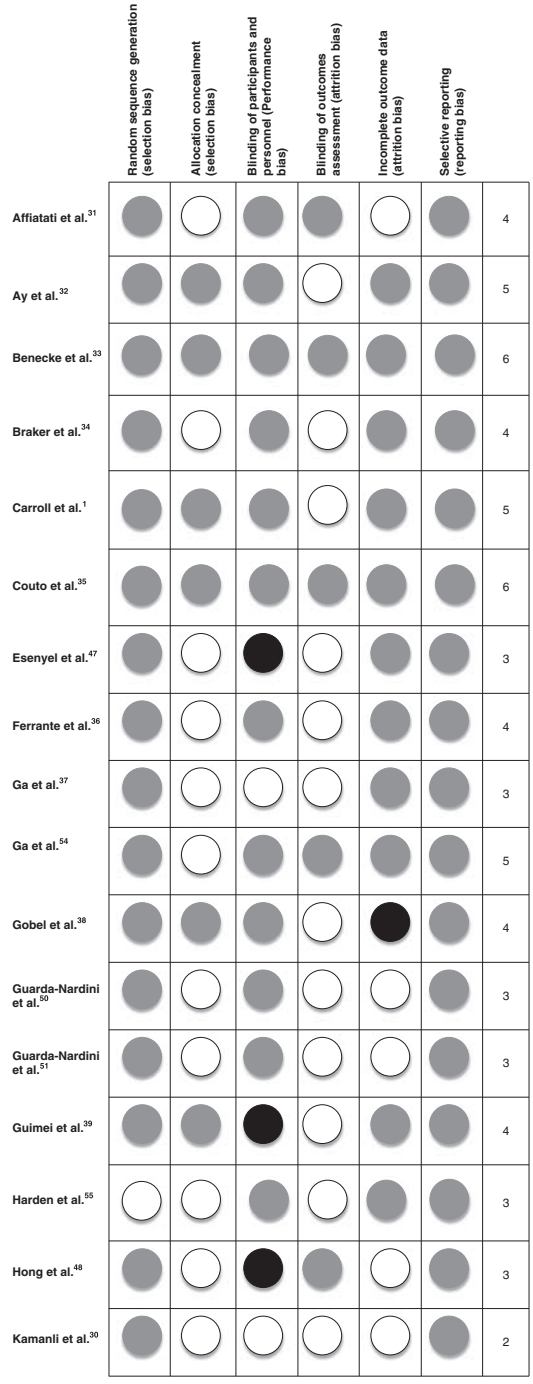

FIGURE 2A. Risk of bias assessment.

18 articles assessed the effect of local anesthetic trigger point injections on reported pain intensity, and a total of 16 articles assessed the effect of BTX-A injections on reported pain intensity. Eighteen of the 33 articles had a low risk of bias on 4 to 6 of the 6 items assessed (Fig. 2A, 2B).[1,31–47]

A qualitative assessment of the results from each study revealed inconsistency in the effectiveness of local anesthetic and BTX-A injections (Supplemental Table 1; Supplemental Digital Content 2, http://links.lww.com/CJP/A555). Eight of the 18 articles assessing the effect of local anesthetics reported statistically significant improvements in pain intensity at 1 to 2, 3 to 4, 7 to 8, 11 to 12, 16, and 24 weeks follow-up.[17,30,31,35,40,47–49] These studies were comprised of 2 saline placebo trials, 1 trial with a placebo local anesthetic patch as a comparator and a lidocaine injection for the experimental intervention, 3 trials with dry needling using a syringe in the experimental and control interventions with and without lidocaine, respectively, 1 trial with a stabilization splint as a comparator and a stabilization splint and lidocaine injection as the experimental treatment, and 1 trial with neck stretching as the

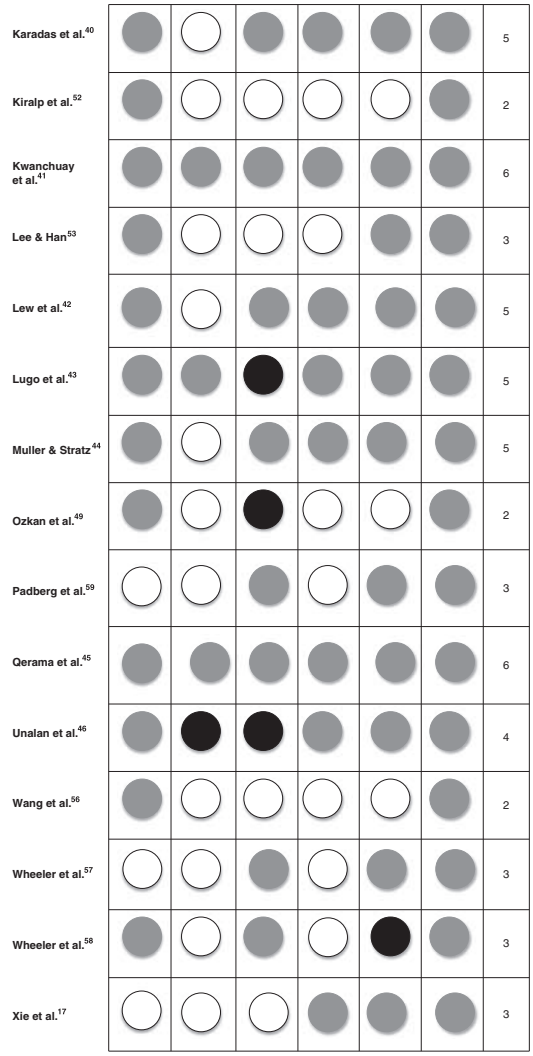

FIGURE 2B. (*Continued*)

comparison group. Four of the 16 articles assessing the effect of BTX-A injections found significant improvements in reported pain intensity at 3 to 4, 5 to 6, 7 to 8, 9 to 10, 11 to 12, and at 24 weeks follow-up.[30,33,38,50] Three of these studies were trials with a saline placebo comparator, and 1 study with dry needling using empty syringes in the control intervention and BTX-A injections in the experimental intervention.

Overall, trigger point injections presented a small to moderate effect size for reducing patient-reported pain intensity at 1 to 2, 3 to 4, 7 to 8, 16, 18, and 24 weeks follow-up (Table 1). The effect size for both trigger point injections was significant only at the 3 to 4 weeks follow-up period ($P = 0.02$).

There was a trend of small and large effect sizes favoring the experimental intervention within the local anesthetic subgroup over follow-up periods, with the exception of 0 and 11 to 12 weeks follow-up, relative to the BTX-A subgroup which consistently showed small effect sizes favoring the control intervention or a negligible effect size favoring the experimental intervention until 16 weeks follow-up (Table 2). At 18 and 24 weeks, BTX-A injections had a small to moderate effect size at reducing reported pain intensity.

0 Week

Data from 5 studies was included in this subgroup, with a total of 5 comparisons in the analysis.[44,46,48,51,52] Heterogeneity among all studies at 0-week follow-up was high $I^2 = 58\%$ ($\chi^2_{df=4} = 9.54$, $P = 0.05$). The SMD for studies assessing local anesthetic injections was negligible favoring the experimental intervention, and large for studies assessing BTX-A injections favoring the control intervention. Heterogeneity was moderate among studies assessing the effect of local anesthetics $I^2 = 37\%$ ($\chi^2_3 = 4.74$, $P = 0.19$) (Fig. 3).

1 to 2 Weeks

Data from 11 studies was included in the analysis for this follow-up period, with a total of 18 observations.[31,35,37,39,48,50,53–58] The heterogeneity among all studies was high $I^2 = 89\%$ ($\chi^2_{18} = 157.64$, $P < 0.001$). The effect size of local anesthetic injections on pain intensity was large and favored the experimental intervention, the effect size of BTX-A injections was small and favored the control intervention. Heterogeneity was high among studies assessing the effect of local anesthetic injections

TABLE 1. SMD Values of Reported Pain Intensity Following Trigger Point Injections at Follow-up

Follow-up Period (wk)	Experimental Sample Size	Control Sample Size	SMD (95% CI)	Heterogeneity (I^2) (%)
0	263	262	0.18 (−0.06, 0.41)	44
1-2	458	459	−0.29 (−0.71, 0.12)	89
3-4	653	667	−0.37 (−0.69, −0.06)*	86
5-6	262	276	−0.04 (−0.21, 0.13)	0
7-8	492	496	−0.28 (−0.74, 0.17)	91
9-10	44	42	−0.07 (−0.57, 0.44)	28
11-12	486	487	−0.05 (−0.34, 0.20)	75
16	121	124	−0.60 (−1.37, 0.17)	87
18	10	9	−0.59 (−1.51, 0.34)	NA
24	118	120	−0.31 (−0.69, 0.07)	51

CI indicates confidence interval; NA, not applicable; SMD, standardized mean difference.
*$P = 0.02$.

$I^2 = 93\%$ ($\chi^2_8 = 120.71$, $P < 0.001$) and BTX-A on patient-reported pain $I^2 = 58\%$ ($\chi^2_9 = 21.28$, $P = 0.01$) (Fig. 4).

3 to 4 Weeks

Data from 16 studies was included in this subgroup, with a total of 24 comparisons.[30,32–36,37,38,41,43,49,50,54,55,57,58] Heterogeneity between all studies in this subgroup was high, $I^2 = 86\%$ ($\chi^2_{23} = 170.04$, $P < 0.001$). The SMD for local anesthetic injections on patient-reported pain was large and favored the experimental intervention. The SMD for BTX-A injections on pain intensity was nil. Heterogeneity among studies assessing the effect of local anesthetic injections was high, $I^2 = 92\%$ ($\chi^2_7 = 82.67$, $P < 0.001$). Heterogeneity was also high among the BTX-A studies, $I^2 = 63\%$ ($\chi^2_{15} = 40.17$, $P < 0.001$) (Fig. 5).

5 to 6 Weeks

Five studies were included into this subgroup, with a total of 11 observations.[34,36,41,55,57] Heterogeneity among these studies was nil $I^2 = 0\%$ ($\chi^2_{10} = 5.02$, $P = 0.89$). Only BTX-A injection studies were included in this follow-up period as there were no follow-up data available for this study period among the local anesthetic injection studies. The SMD for these studies negligibly favored the experimental intervention (Fig. 6).

7 to 8 Weeks

Data from 8 studies was included in this subgroup.[17,33,36,38,40,55,56,58] A total of 14 observations were included in this subgroup. Heterogeneity among all studies assessing patient-reported pain at 7 to 8 weeks follow-up was high, $I^2 = 91\%$ ($\chi^2_{13} = 151.26$, $P < 0.001$). The SMD of local anesthetics on patient-reported pain was large and favored the experimental intervention, and the SMD for the BTX-A intervention favored the experimental intervention negligibly. The heterogeneity among the local anesthetic studies was high, $I^2 = 98\%$ ($\chi^2_3 = 131.48$, $P < 0.001$). The heterogeneity among the BTX-A studies was moderate, $I^2 = 37\%$ ($\chi^2_9 = 14.33$, $P = 0.11$) (Fig. 7).

9 to 10 Weeks

Data from 3 studies were included in this subgroup, with a total of 4 observations.[34,55,57] Only BTX-A data were

TABLE 2. SMD Values of Reported Pain Intensity Within the Local Anesthetic and BTX-A Injection Interventions at Follow-up

SMD Effect Size Within Local Anesthetics and BTX-A Subgroups Across Follow-up Periods								
	Local Anesthetics				BTX-A			
Follow-up Period (wk)	Experimental Sample Size	Control Sample Size	SMD (95% CI)	I^2 (%)	Experimental Sample Size	Control Sample Size	SMD (95% CI)	I^2 (%)
0	151	142	0.13 (−0.23, 0.49)	63	112	120	0.24 (−0.06, 0.54)	22
1-2	220	206	−0.96 (−1.80, −0.13)*	93	238	253	0.21 (−0.07, 0.50)	58
3-4	205	211	−1.01 (−1.76, −0.27)*	92	448	456	0.00 (−0.24, 0.23)	63
5-6	No data	No data	No data	No data	262	276	−0.04 (−0.21, 0.13)	0
7-8	111	109	−1.27 (−3.50, 0.96)	98	381	387	−0.03 (−0.21, 0.16)	37
9-10	No data	No data	No data	No data	44	42	−0.07 (−0.57, 0.44)	28
11-12	141	139	−0.07 (−1.11, 0.96)	94	347	348	−0.09 (−0.24, 0.06)	0
16	78	78	−1.33 (−2.11, −0.55)‡	79	43	46	0.24 (−0.18, 0.66)	0
18	No data	No data	No data	No data	10	9	−0.59 (−1.51, 0.34)	NA
24	98	101	−0.31 (−0.82, 0.21)	70	20	19	−0.33 (−0.96, 0.31)	0

BTX-A indicates botulinum toxin-A; CI, confidence interval; NA, not applicable; SMD, standardized mean difference.
*$P < 0.05$.
‡$P < 0.001$.

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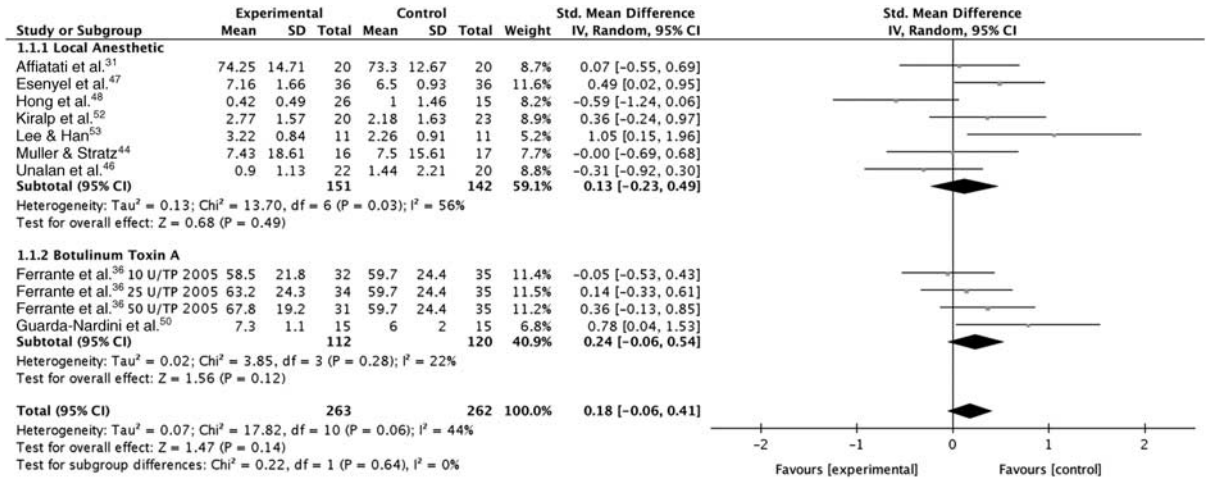

FIGURE 3. Subgroup analysis of local anesthetic and BTX-A MTrP injections on patients reported pain immediately after injection. BTX-A indicates botulinum toxin-A; CI, confidence interval; MTrP, myofascial trigger points.

available from the included studies for this follow-up period. Heterogeneity among studies in this subgroup was moderate $I^2 = 28\%$ ($\chi^2_3 = 4.16$, $P = 0.24$) (Fig. 8). The SMD negligibly favored the experimental intervention.

11 to 12 Weeks

Data from 13 studies were included in this subgroup, with a total of 16 observations.[32–34,36,38,43,49,51,55,56–59] Heterogeneity among all studies was high, $I^2 = 75\%$ ($\chi^2_{15} = 60.55$, $P < 0.001$). The SMD of local anesthetic and BTX-A injections on patient-reported pain negligibly favored the experimental intervention. Heterogeneity among the studies assessing the effect of local anesthetic injections was high, $I^2 = 94\%$ ($\chi^2_3 = 50.79$, $P < 0.001$). Heterogeneity among articles assessing the effect of BTX-A was nil $I^2 = 0\%$ ($\chi^2_{11} = 9.74$, $P = 0.55$) (Fig. 9).

16 Weeks

Four studies were included in this subgroup with a total of 6 observations.[17,40,57,58] Heterogeneity among all studies was high $I^2 = 87\%$ ($\chi^2_5 = 39.42$, $P < 0.001$). The SMD for the local anesthetic injections was large and favored the experimental intervention, whereas the SMD for the BTX-A studies was small and favored the control intervention. Heterogeneity among the studies assessing the effects of local anesthetic injections was high $I^2 = 79\%$ ($\chi^2_2 = 9.63$, $P < 0.001$). The heterogeneity of the studies assessing the effects of BTX-A was nil $I^2 = 0\%$ ($\chi^2_2 = 1.63$, $P = 0.44$) (Fig. 10).

18 Weeks

Data from 1 study were included in this subgroup, this study assessed the effects of BTX-A injections.[34] The SMD was moderate and favored the experimental intervention.

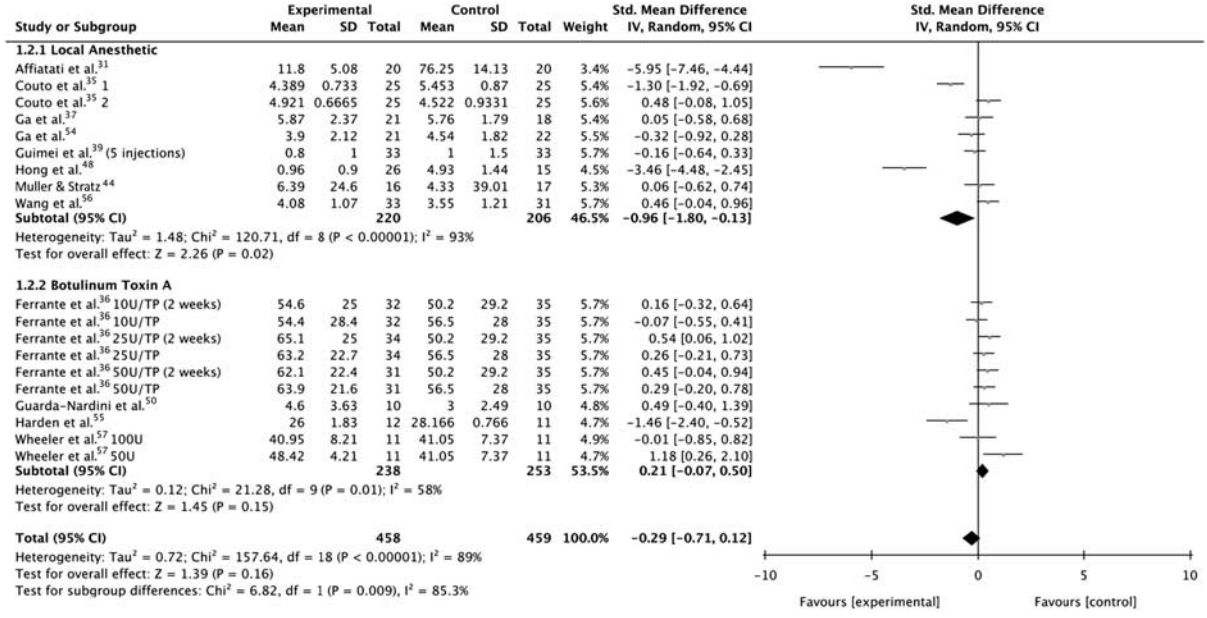

FIGURE 4. Subgroup analysis of local anesthetic and BTX-A MTrP injections on patients reported pain 1 to 2 weeks after injection. BTX-A indicates botulinum toxin-A; CI, confidence interval; MTrP, myofascial trigger points.

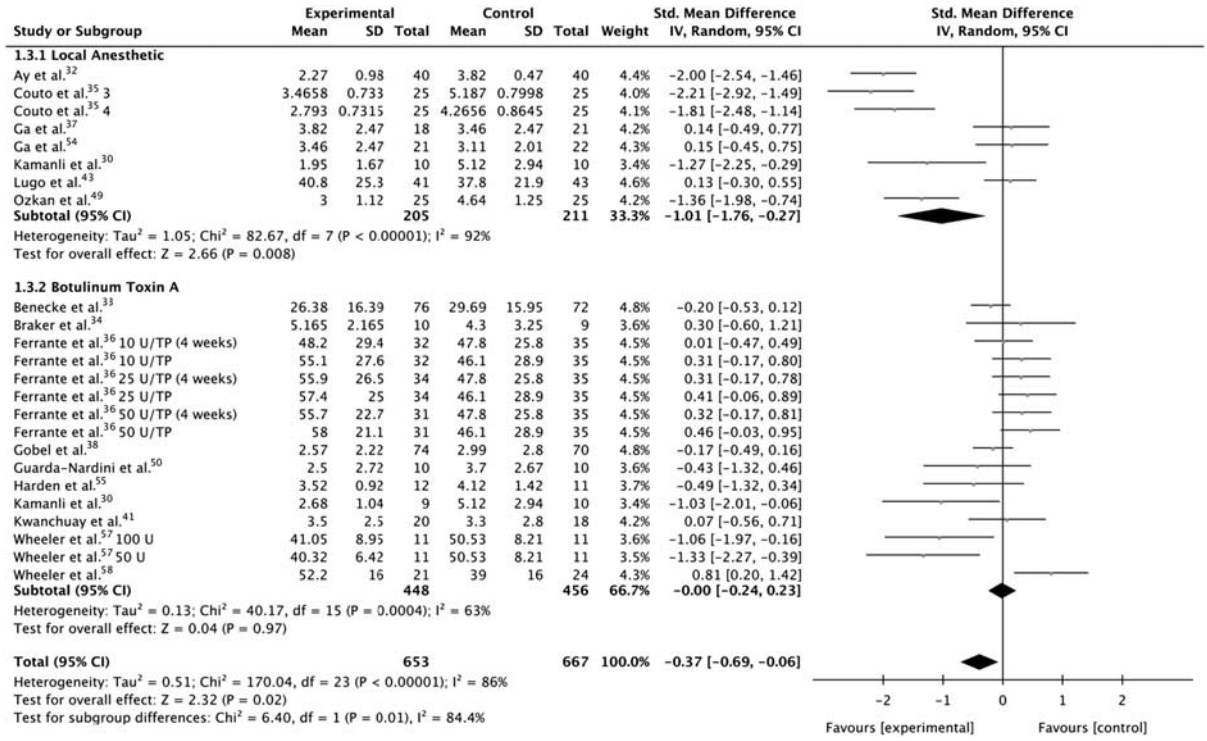

FIGURE 5. Subgroup analysis of local anesthetic and BTX-A MTrP injections on patients reported pain 3 to 4 weeks after injection. BTX-A indicates botulinum toxin-A; CI, confidence interval; MTrP, myofascial trigger points.

24 Weeks

Five studies were included in this subgroup, with a total of 6 observations recorded.[17,34,40,50,52] The overall SMD was small and favored the experimental intervention. Heterogeneity among studies assessing the effects of local anesthetic and BTX-A was moderate $I^2 = 51\%$ ($\chi^2_5 = 10.27$, $P = 0.07$). The SMD of studies assessing the effect of local anesthetic injections as well as the BTX-A studies was small and favored the experimental intervention. Heterogeneity among the studies assessing the effects of local anesthetic injections was high $I^2 = 70\%$ ($\chi^2_3 = 10.00$, $P = 0.02$). Heterogeneity among the studies assessing the effect of BTX-A injections was nil $I^2 = 0\%$ ($\chi^2_1 = 0.27$, $P = 0.60$) (Fig. 11).

Subgroup Analysis by Number of Injection Sessions and Region of Injection

The subgroup analysis assessing the effect of 1 and multiple injection sessions of local anesthetics or BTX-A revealed a moderate effect size on pain intensity with 1 session of local anesthetic injections and a large effect size for multiple sessions of local anesthetic injections (Table 3). Both effect sizes favored the experimental intervention.

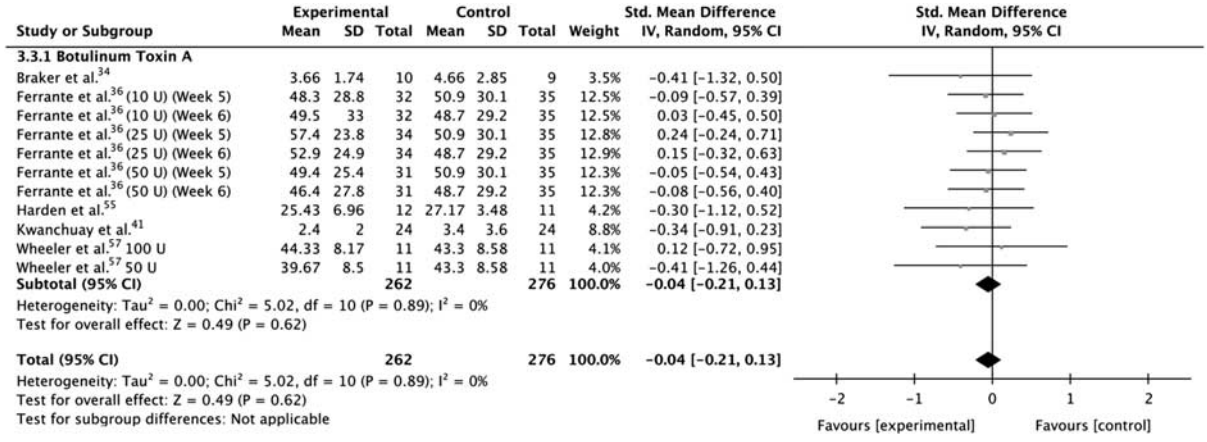

FIGURE 6. Subgroup analysis of local anesthetic and BTX-A MTrP injections on patients reported pain 5 to 6 weeks after injection. BTX-A indicates botulinum toxin-A; CI, confidence interval; MTrP, myofascial trigger points.

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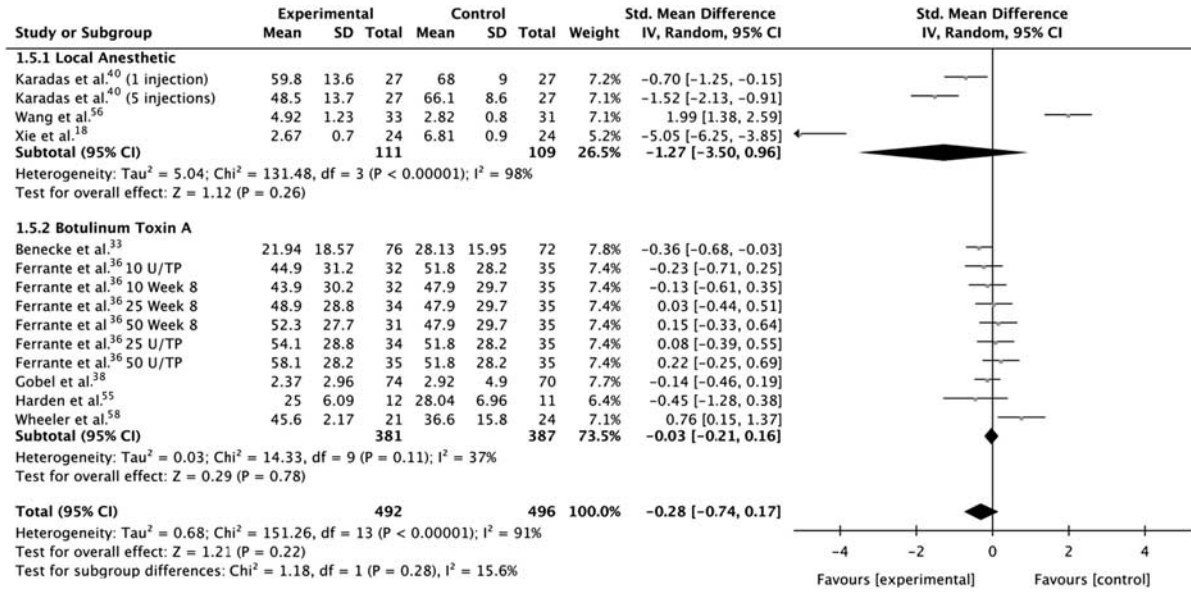

FIGURE 7. Subgroup analysis of local anesthetic and BTX-A MTrP injections on patients reported pain 7 to 8 weeks after injection. BTX-A indicates botulinum toxin-A; CI, confidence interval; MTrP, myofascial trigger points.

The effect size for a single session of BTX-A was negligible and favored the control intervention. There were no studies that delivered multiple BTX-A injections.

The subgroup analysis assessing the effect of local anesthetic injections and BTX-A injections at the cervical and shoulder muscles revealed a small effect size favoring the experimental intervention for local anesthetic injections and a negligible effect size for BTX-A injections. The effect size for local anesthetic injections at the temporomandibular joint muscles was large and favored the experimental intervention. The effect of BTX-A injections at the temporomandibular joint muscles was marginally small and favored the experimental intervention. Studies that assessed the effect of local anesthetic injections at widespread body regions revealed a large effect size that favored the experimental intervention. There were no studies that assessed the effect of BTX-A injections in widespread pain.

DISCUSSION

Results from our meta-analysis suggest that local anesthetic injections have a more favorable effect relative to BTX-A injections at reducing reported pain intensity among individuals with myofascial pain. Local anesthetics showed a consistent large effect size for improvement at 1 to 2, 3 to 4, 7 to 8, and 16 weeks follow-up, whereas BTX-A injections presented with negligible or small effect sizes during these follow-up periods. At 11 to 12 weeks follow-up, local anesthetics demonstrated with a negligible effect size favoring the experimental intervention. This can be mainly attributed to findings from Wang et al's[56] study whereby the effect of lidocaine trigger point injections was compared with mini-scalpel needling and showed a large effect size favoring the mini-scalpel needing intervention. Within this follow-up period, other studies assessing the effect of local anesthetics had small to large favorable effect sizes favoring local anesthetic injections (Fig. 9). The effect size for local anesthetic injections was small at 24 weeks follow-up, favoring local anesthetic injections. Our results also suggest that local anesthetics are more effective at reducing patient-reported pain when injections are localized to the temporomandibular muscles (SMD = −1.01) and generalized muscles (SMD = −1.41) in the body. BTX-A injections showed moderate and small effect sizes favoring the BTX-A intervention at 18 and 24 weeks follow-up; however, given the consistency of the results indicating a negligible effect or

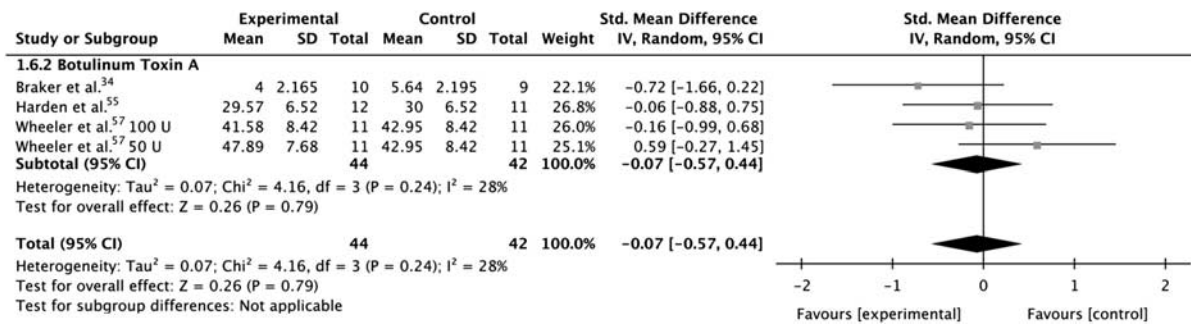

FIGURE 8. Subgroup analysis of local anesthetic and BTX-A MTrP injections on patients reported pain 9 to 10 weeks after injection. BTX-A indicates botulinum toxin-A; CI, confidence interval; MTrP, myofascial trigger points.

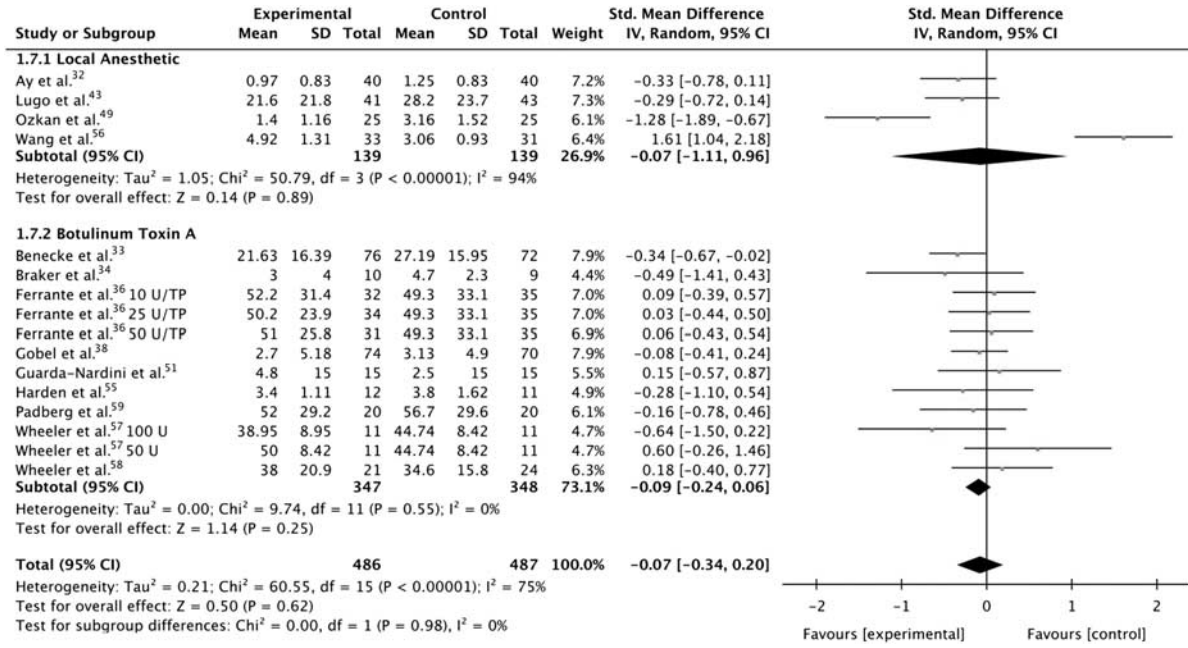

FIGURE 9. Subgroup analysis of local anesthetic and BTX-A MTrP injections on patients reported pain 11 to 12 weeks after injection. BTX-A indicates botulinum toxin-A; CI, confidence interval; MTrP, myofascial trigger points.

small effect size favoring the control intervention for BTX-A injections before 18 weeks, it may be a sampling effect that resulted in these findings.

The mechanism of action for each injectate and the location at which the injectates are delivered may account for the observed effect differences between local anesthetics and BTX-A. As discussed above, the formation and maintenance of MTrPs is thought to occur through a mechanism of spinal facilitation, whereby abnormal motor endplate activity causes an energy crisis in a region of muscle and results in a local contracture known as a taut band that can develop into an MTrP.[11,60] Persistent nociceptive afferent input from the MTrP results in central sensitization at the spinal cord and efferent output that maintains the MTrP. In addition, the MTrP releases inflammatory and algogenic substances that further contribute to the sensitized state of the MTrP.[60] The hypersensitivity and allodynia found at active MTrPs—MTrPs that induce pain—suggests that both nociceptive and non-nociceptive sensory neurons are sensitized at the region of the MTrP.[11] Wang et al[56] and Meng et al[15,16] found that large diameter myelinated neurons contribute to the pain experience at MTrPs, as blocking their signals increased pain thresholds and reduced spontaneous electrical activity (SEA) at the region of the trigger point. SEA is associated with increased pain at the region of the MTrP and is thought to be caused by abnormal motor endplate as well as muscle spindle activity.[9] Because of the mechanism of action of local anesthetics and BTX-A, it may be more effective for local anesthetics to be injected at the MTrP as well as the motor endplate region associated with the location of muscle pain. In contrast, it may be more beneficial for BTX-A to be injected at the motor endplate

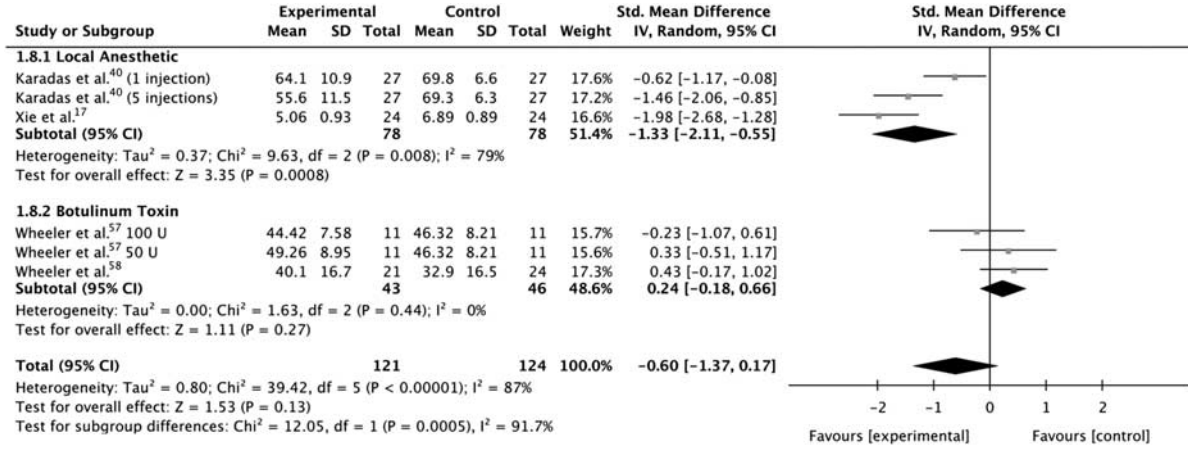

FIGURE 10. Subgroup analysis of local anesthetic and BTX-A MTrP injections on patients reported pain 16 weeks after injection. BTX-A indicates botulinum toxin-A; CI, confidence interval; MTrP, myofascial trigger points.

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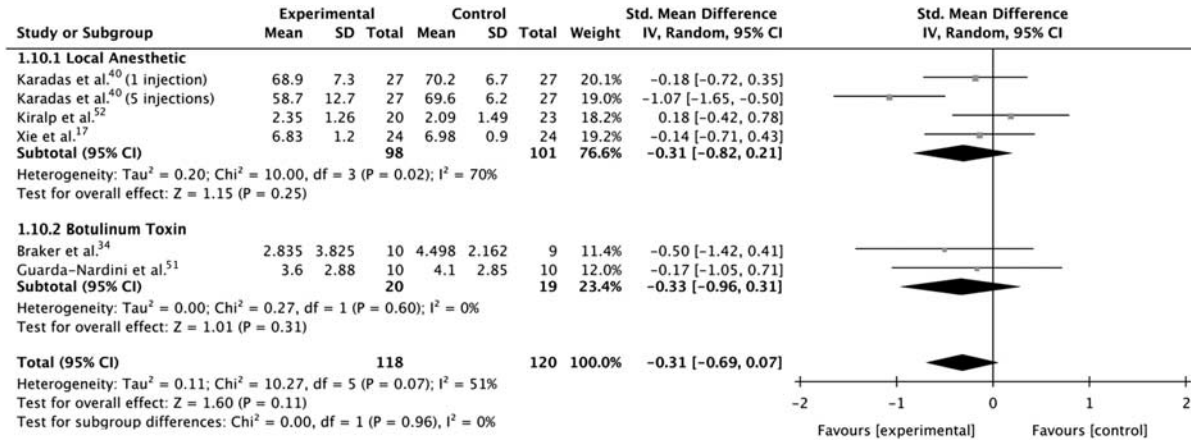

FIGURE 11. Subgroup analysis of local anesthetic and BTX-A MTrP injections on patients reported pain 24 weeks after injection. BTX-A indicates botulinum toxin-A; CI, confidence interval; MTrP, myofascial trigger points.

region only. Local anesthetics are used to block the afferent and efferent sensory motor signals at the sensitized neurons within the region of the MTrP, with the aim of reversing the central sensitization associated with the MTrPs.[11,58] This is thought to disrupt the spinal facilitation arc contributing to the maintenance of the MTrP and reduce pain signals. Disrupting this spinal mechanism should relax the taut band or MTrPs' contractility as well as increase blood flow to the region of the taut band or MTrP, thereby providing oxygen and ATP to improve local ischemia which can further reverse the contractile state. Blocking signals from motor endplate units should also reduce the excessive acetylcholine release contributing to the contractile state within the region of the taut band or MTrP. Xie et al[17] also found that injecting lidocaine at the motor endplate unit associated with MTrPs and muscle pain resulted in significantly reduced patient-reported pain relative to injecting lidocaine directly at the MTrP.

BTX-A acts by retrogradely inhibiting intracellular calcium-mediated vesicle exocytosis, effectively reducing the release of acetylcholine at the neuromuscular junction and subsequently muscle contractility.[61] This has been shown to reduce SEA and pain at the region of the MTrP. BTX-A was also proposed to act on large diameter sensory afferents that innervate 1a intrafusal muscle fibers, which are associated with proprioceptive sensation and contractile responses. Blocking these afferent signals has been shown to reduce the severity of dystonia, and theoretically should reduce the contractile state of a taut band or MTrP.[62] Our analyses revealed that BTX-A did not result in any substantial benefit on reported pain at most follow-up periods, and only 4 studies found significant differences favoring the BTX-A injections between 3 to 12 weeks follow-up.[30,33,38,50] It is possible that BTX-A would result in more beneficial effects if injected at the region of motor endplate units rather than within taut bands or MTrPs. Barbero et al[62] found that MTrPs are located within a 10-mm vicinity from motor endplate units, therefore injecting BTX-A at a proximal region surrounding the MTrP or the localized painful taut band may be more effective. The effects of injection location (motor point versus MTrP or taut band) necessitates further investigation.

The subgroup analysis assessing the effectiveness of BTX-A at different muscle regions found that BTX-A had a marginally small and significant effect size at reducing reported pain when injected at temporomandibular muscles

TABLE 3. Subgroup Analyses for by Number of Injection Sessions and Region of Injection Within Local Anesthetic and BTX-A Injection Interventions

	Local Anesthetic (Effect Size)	Heterogeneity	BTX-A (Effect Size)	Heterogeneity
Subgroup analysis by no. injection sessions				
1 session	−0.51 (−0.94, −0.08)*	$I^2 = 92\%$ ($\chi^2_{21} = 263.18$, $P < 0.001$)	0.02 (−0.05, 0.08)	$I^2 = 38\%$ ($\chi^2_{72} = 115.97$, $P < 0.001$)
Multiple sessions	−0.86 (−1.45, −0.26)*	$I^2 = 93\%$ ($\chi^2_{16} = 220.46$, $P = 0.005$)	No data	No data
Subgroup analysis by region of injection				
Cervical and shoulder muscles	−0.44 (−0.82, −0.07)*	$I^2 = 92\%$ ($\chi^2_{29} = 346.69$, $P < 0.001$)	0.01 (−0.05, 0.08)	$I^2 = 39\%$ ($\chi^2_{67} = 109.53$, $P < 0.001$)
Temporomandibular joint muscles	−1.01 (−1.35, −0.67)§	$I^2 = 63\%$ ($\chi^2_{7} = 18.98$, $P < 0.001$)	−0.19 (−0.35, −0.03)*	$I^2 = 32\%$ ($\chi^2_{8} = 11.76$, $P = 0.16$)
Widespread (unspecified)	−1.41 (−2.45, −0.38)*	$I^2 = 94\%$ ($\chi^2_{6} = 105.50$, $P < 0.001$)	No data	No data

BTX-A indicates botulinum toxin-A.
*$P < 0.05$.
§$P < 0.001$.

(SMD = −0.19), whereas BTX-A injections at the cervical and shoulder muscles had no effect (SMD = 0.01). This could be due to the close proximity of motor points within the temporomandibular muscles. In addition, BTX-A is more effective at regions with frequently used muscles and therefore may have been more effective at the temporomandibular muscles as they are used extensively with daily activities.[61] As the goal of our study was to assess the effects of intramuscular injections at regions of muscle pain and MTrPs, the potential for bias to be present based upon drug mechanism of action exists. Local anesthetics may have shown a superior effect as they act to inhibit both afferent and efferent neurons. Theoretically, by impacting both afferent and efferent components more effective reduction in pain and sensitization may occur. In contrast, BTX-A inhibits acetylcholine release at the neuromuscular junction and is not known to act upon the afferent neurons. Therefore, it is likely more beneficial for BTX-A to be injected at motor points as the concentration of neuromuscular junctions is highest at the motor point and not within the MTrP or taut band.

The subgroup analysis comparing the effect of a single or multiple injection sessions of local anesthetics revealed a significant moderate effect size (SMD = −0.51) and significant large effect size (SMD = −0.86) favoring the local anesthetic injection intervention after a single session and multiple sessions of injections, respectively. The studies included in this review for BTX-A were limited to one injection session trial, which showed a negligible effect size (SMD = 0.02). Additional studies are needed to determine the effectiveness of multiple BTX-A injections. Our study results cannot provide conclusions on the optimal quantity and concentration of local anesthetic injections at each location of muscle pain. This is because the studies that found significant improvements in reported pain were limited in number and varied in their type of injected local anesthetic, comparison groups, and importantly their reporting of quantities injected.[17,30,31,35,40,47–49] All the BTX-A trials in this review underwent a single session of BTX-A injections, and therefore no conclusions can be made about the optimal number of BTX-A injections. However, studies that found beneficial effects for BTX-A injected between 10 and 40 units of BTX-A into each MTrP. Comparatively, only Ferrante et al[36] performed a study assessing the effectiveness of MTrP injections with 10, 25, 50 units, or saline at the cervical and shoulder muscles, and found no significant difference between groups.

Further studies should also assess whether the location of injection (MTrP, motor endplate neurons) for each type of injectate influences patient outcomes, and whether different quantities are required depending on the muscle being injected—as BTX-A had been reported to be more effective at frequently contracted muscles.[61] Our results suggest that BTX-A is marginally effective at reducing subjective pain associated with the temporomandibular joint muscles. In addition, local anesthetics were found to be effective at reducing pain intensity at the cervical and shoulder muscles, temporomandibular muscles, and generalized muscles in the body.

Implications for Clinical Practice

Currently, there are no accepted guidelines for the injection treatment of myofascial pain. Wheeler[63] has published recommendations for MTrP injection treatment, as well as other pharmacologic treatments for myofascial pain. Wheeler[63] reports that 0.5% to 2.0% lidocaine, 1.0% to 1.5% of mepivicaine, and 0.25% to 0.5% of bupivacaine is used at a maximum single dose of 500, 500, and 200 mg for each injectate, respectively. Local anesthetic injections ranged in quantity and concentration across studies in this review. The concentration of local anesthetic injectates ranged between 0.3 % to 2.0 % across the included studies. Several studies among those that found significant improvements in pain intensity reported the quantity of injectate they used, which ranged between 2 to 5 mg. Cummings et al[64] reported more lasting beneficial effects for bupivacaine and ropivicaine when injected with dexamethasone, this should be considered when guidelines are developed for local anesthetic injections at taut bands and MTrPs. Wheeler[63] also recommended the injection of 2.5 to 20 units of BTX-A (Botox) per trigger point in the cervical and back muscles. Studies included in this review that found a beneficial effect for BTX-A injections at the cervical and shoulder muscles delivered a total of 10 to 400 units of BTX-A. The injection quantity per trigger point ranged between 10 and 40 units, exceeding the recommended dosage by Wheeler.[63] One study found that BTX-A injections at temporomandibular muscles were effective at 24 weeks follow-up; they delivered a total of 100 units of BTX-A with 25 units per muscle about the temporomandibular joint. This review's results and Wheeler's[63] recommendations suggest that there is a range of local anesthetic and BTX-A injection doses that would provide the most benefit for patients with myofascial pain. There is a need to update Wheeler's[63] recommendations, and to collate available evidence on injection therapy into a single updated evidence-based guideline for clinicians. We recommend the development of clinical guidelines specifying the quantity and frequency of therapeutic injections for myofascial pain.

Overall, the results of this study suggest a few key points for clinical practice. Local anesthetics presented a stronger effect at mitigating subjective pain severity relative to BTX-A injections when compared with placebo, this effect was consistent until 16 weeks posttreatment. Multiple injections of local anesthetics seemed to offer more pain relief relative to single injections. The effects of BTX-A injections are uncertain based on the results of the study, given the negligible effect sizes. This finding may be mediated by the limited number of studies assessing the effects of BTX-A as well as the location of BTX-A injection—whereby it is possible that injecting motor endplate regions would be more effective as BTX-A's mechanism of action is in line with that of MTrP pathophysiology. Temporomandibular muscles seemed to benefit more from local anesthetics or BTX-A injections relative to other muscle groups. Clinically, patients seem to respond to both local anesthetic and BTX-A injections. Studies that have compared the efficacy of the 2 injectates have found similar results in terms of pressure pain threshold and subjective pain severity improvement.[19,30] Kamanli et al[30] found significant improvements in depression and anxiety measure scores following BTX-A injections, and no effect in the local anesthetic or dry needling comparison groups. This suggests that the clinical profile of patients with myofascial pain may differ, and responsivity may differ based on clinical presentation. Therefore, although this study found local anesthetics to be effective at mitigating pain severity ratings, there needs to be further investigation into the clinical correlates that predict the success of local anesthetic and BTX-A injections. We believe the following clinical correlates

should be considered in future studies: pain, range of motion, strength, measures of disability, and handicap as well as important clinical outcomes such as return to work or sport. These considerations should also be included in updates and revisions of MTrP injection guidelines such as those proposed by Wheeler.[63]

A few studies reported adverse events (AEs) following local anesthetic or BTX-A injections, with others reporting no adverse events. Reported AEs in studies administering local anesthetic injections were subcutaneous hemorrhage, dizziness, muscle soreness, transient hypertension which relieved after brief rest, insomnia, coldness, and burning at the injection site, paresthesias, pain at the injection site, cervical muscle spasm, localized hematomas, and minimal bleeding.[30,34,37,39,40,43,48,54] AEs among the studies delivering BTX-A included transient pain and weakness, muscle soreness, minor discomfort with chewing, redness surrounding the injection site, feeling feverish, tightness at the injected site, stiffness at the shoulder associated with the injection site, fatigue, headache, heaviness, and numbness.[1,30,38,41,50,57–59] Gobel et al[38] reported that the AEs they observed presented at ~1 to 2 months, and most dissipated. It is possible that the timing of AE presentation may have masked some of the benefit incurred from the BTX-A treatment on subjective pain, accounting for the latent benefit observed for BTX-A injections. The studies overall seemed to suggest that these events were transient in nature.

Overall, we recommend that the comprehensive management of a patient with MPS should include careful attention to the basic principles of pain management. This includes nonpharmacological treatments using appropriate combinations of rest and allied health care (physiotherapy, chiropractic, occupational therapy, and massage therapy). Ideally, these treatments should be considered before injection treatments to minimize AEs and maximize patient benefit. When the decision has been made clinically to inject the region of the trigger point, we recommend ultrasound guidance as well as following the protocol we previously published.[65] The current study provides the clinical with some guidance about the injectate.

Limitations

This is the first systematic review to compare the effectiveness of local anesthetic and BTX-A injections on reported pain intensity among patients with myofascial pain. Three large databases were searched using broad terms for myofascial pain and various injectate terms for local anesthetics and BTX-A, ensuring a comprehensive assessment of the literature. A limitation in our findings is the high heterogeneity among studies, notably among studies assessing the effects of local anesthetic injections. This can be attributed to the variability in the type of local anesthetic injectates given (lidocaine, bupivacaine, and prilocaine), variation in study design (randomized controlled trial, controlled trial, randomized trial), the diversity of injected muscles, and the variety of adjunct treatments given to participants. Among the studies assessing the effects of BTX-A, all studies had a saline control with the exception of 2 studies that had a dry needling and fascial manipulation control. Of the 18 studies in the local anesthetic injections meta-analysis, 3 studies delivered the same alternative intervention to the experimental and comparison group—neck stretching, physical therapy, stabilization splint—but added local anesthetic injections to the experimental group allowing for the study of the additional effects of the local anesthetic injection. Two studies among the local anesthetic studies had a saline control group, and 5 studies delivered identical dry needling to the experimental and control group but added a local anesthetic injectate to the experimental group. Eight studies had alternative treatment comparison groups; lidocaine patch, intramuscular stimulation therapy, acupuncture, bloodletting, dry needling, laser therapy, miniscalpel needling, proprioceptive neuromuscular facilitation, tropisetron injection, and high-power pain threshold ultrasound therapy. These alternative treatment studies present a limitation to our study results as the comparison did not deliver a similar vehicle intervention (syringe needling) as the injection intervention. The reader should recognize this as a significant source of heterogeneity in the local anesthetic results; however, the effect sizes for most of the studies assessing the effects of local anesthetic injections favored the experimental intervention at time periods following 0 week suggesting that local anesthetic injectates are indeed an effective treatment. A few studies used adjunctive treatments to the experimental and control interventions including oral analgesics from multiple classes such as amitriptyline or ibuprofen, muscle exercise, postural adjustments, heat, and ultrasound therapy presenting another avenue for heterogeneity in the observed results.[30,36,37,41,43,48,52,53,55] In addition, the goal of our study was to perform a comprehensive review of all studies that were randomized and or/controlled regardless of their comparison groups, as alternative treatments are commonly used concurrently with injections in practice, to gauge the effectiveness of these interventions. This review was limited to English studies only which may also have biased the findings.

CONCLUSIONS AND FUTURE DIRECTIONS

Overall, the results from this meta-analysis suggest that local anesthetic injections within the region of taut bands or MTrPs are effective at reducing patient-reported pain. Studies utilizing BTX-A did not present favorable effects; however, the location of injection (MTrP or motor endplate region) may have influenced these results and necessitates further investigation. The heterogeneity observed among studies both qualitatively and quantitatively may be attributed to methodological differences between studies as discussed; however, clinical and pathophysiological differences between participants with myofascial pain should also be considered when assessing responsiveness to treatment. For example, Benecke et al[33] found a 49% responders rate among myofascial pain patients who received BTX-A injections, which is poor with regard to patient outcome predictability and recommendations for treatment. Muller and Stratz[44] found that 80% of participants with myofascial pain and tendinopathies experienced some degree of improvement following lidocaine and dexamethasone injections, with 20% experiencing notable improvement in pain. These differences in injection responsivity may be attributed to differences in the pathophysiology and etiology underlying myofascial pain. The integrated hypothesis suggests that myofascial pain is induced by external muscle stressors; however, an alternate hypothesis postulates a neurogenic basis for myofascial pain where MTrPs are a manifestation of central sensitization.[60] It is possible that individuals presenting with endogenously or exogenously initiated myofascial pain respond variably to different injection treatments. This presents an avenue for future

research, and may guide the decision making of clinicians as well as assist in the development of therapeutic guidelines for myofascial pain. Finally, the effect of localized injections should be assessed in conjunction with other interventions that may augment their effectiveness such as alternative physical therapies or added dexamethasone. This review included studies that assessed stretching and strengthening, stabilization splints, needling, and manipulation treatments as comparators and/or added treatments to injections. However, findings between these studies is limited and heterogenous, warranting further studies and replication. Additional exercise interventions such as aerobic exercise, which promotes overall vascular flow and has been shown to reduce pain in patients with myofascial pain, should be assessed in comparison and in conjunction to injections as exercise presents a feasible treatment and is beneficial for the overall physical condition of patients with pain.[66]

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