Botulinum Toxin Injection for Pain in Muscle Spasm and Visceromotor Disorders: A Meta-Analysis

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ABSTRACT

Background Apart from the popular use of botulinum neurotoxin type A (BoNT/A) for neuro-rehabilitation and cosmetic purposes, its analgesic potential has been highlighted in various studies. Although BoNT/A is effective, there is a paucity of literature explicating its effectiveness on muscle-based and visceromotor pain.

Objective This meta-analysis determined the effectiveness of botulinum type A (BoNT-A) in treating muscle-based (nociceptive) and visceromotor pain.

Data Sources Studies were searched at PubMed, ScienceDirect, EBSCO Host, and Google Scholar. Unpublished literature was also searched through ProQuest Dissertations & Theses Database and ClinicalTrials.gov.

Review Methods Randomized controlled trials (RCTs) and experimental studies on the effect of botulinum toxin on muscle-based pain were included. An abstraction form was independently accomplished by two reviewers. The standardized mean difference was used as the effect measure using the random-effects model and computed with RevMan 5.3.

Results A total of 17 RCTs were included and analyzed. The standardized mean difference was –0.40 (95%CI: –0.67, –0.13), statistically favoring the BoNT-A group (z=2.94, p = 0.003). Findings also showed a significantly (χ^2=66.56, p<0.00001) large heterogeneity (I^2=74%; τ^2=0.21). Subgroup analyses according to dose concentration and length of follow-up visits showed lower pain scores in the BoNT-A group with a dose less than 300 units (z=2.49, p = 0.01) and a follow-up period greater than 12 weeks (z=2.31, p = 0.02).

Conclusion BoNT-A injections are effective in treating muscle-based (nociceptive) and visceromotor pain disorders.

Keywords: Botulinum neurotoxin, BoNT-A, pain, muscle-based pain, visceromotor pain.

INTRODUCTION

Botulinum neurotoxin is produced by the anaerobic bacterium *Clostridium botulinum* (19). Its strains produce seven antigenically distinct neurotoxins designated as serotonin types A-G (19). All serotypes have a similar structure and molecular weight consisting of a heavy (H) chain and a light (L) chain joined by a disulfide bond (19). They interfere with neural transmission by blocking the release of acetylcholine, the principal neurotransmitter found at the neuromuscular junction (19). After the transmission is blocked by botulinum toxin, the muscles eventually become

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clinically weak and atrophic (19). The nerve terminals do not degenerate, but the blockage of neurotransmitter release is irreversible (19). The function can be recovered by the sprouting of nerve terminals and formation of new synaptic contacts; which usually takes around two to three months (19).

Synthesized as a single chain polypeptide, botulinum toxin has a relatively low potency until it is cleaved by trypsin or bacterial enzymes. The action of botulinum toxin involves a four-step process: (1) high affinity, serotype-specific binding by the heavy chains to receptors on presynaptic membranes of cholinergic nerve endings; (2) receptor-mediated, energy-dependent internalization of the complex (endocytosis); (3) translocation from the acidic endosome of the cytosol; and (4) enzymatic cleavage by the light chain, a zinc-dependent protease, of selected proteins that are critical for fusion of the presynaptic acetylcholine vesicle with the presynaptic membrane, thus preventing the release of acetylcholine into the synapse (9).

Botulinum Neurotoxin Type A, abbreviated as BoNT/A, is one of the most potent biological neurotoxins ever discovered with an estimated intravenous median lethal dose of 1 ng/kg (18). This neurotoxin is produced by the Gram-positive, rod-shaped, anaerobic bacterium *Clostridium botulinum* and other species of the *Clostridia* family (*C. butyricum, C. baratii, and C. argentinense*) (18). BoNT is a complex protein with two distinct parts: the *neurotoxic part* which proteolytically aims at the synaptic proteins involved in vesicular neurotransmitter release and the auxiliary protein part. By and large, there are seven well-known antigenically distinct serotypes of BoNT, that is from BoNT/A to BoNT/G (18). Even in low doses, intravenous administration of this toxin, especially BoNT/A, BoNT/B, and BoNT/E can cause botulism in humans and potentially lead to death.

Albeit the dreadful effect of the botulinum toxin, the advent of medical technology paved the way for purification of the toxin so that it can be used for various medical purposes. Apart from the mainstream usage of botulinum toxin for cosmetic purposes, as in the management of wrinkles, the toxin has been used as a treatment option in different neuromuscular and autonomous disorders (18). In 1987, Brin et al. (2) reported that 14 of 19 (74%) patients who had been treated with BoNT for cervical dystonia experienced pain relief. Further, Binder et al. (3) showed that migraineurs who received BoNT to treat hyperfunctional facial lines experienced improvements in migraine headache after BoNT injection. These results engaged researchers to further assess the efficacy of BoNT injection in the treatment of headache and other types of pain. To alleviate pain associated with numerous neurological conditions, BoNT injections have been used at predetermined fixed sites, irrespective of the site of pain, i.e., specifically targeted to the sites of pain, which is referred to as 'following the pain' technique (28).

Most of the literature suggested that BoNT is useful for analgesic purposes in many musculoskeletal pains such as myofascial pain, low back pain, temporomandibular joint disorders, osteoarthritis, headache (27) and pelvic pain in women (4). Despite the documented efficacy of BoNT/A in dealing with a range of pain disorders, there is a paucity of literature illustrating its significant efficacy in muscle-based (nociceptive) type of pain. Hence, this meta-analysis was conducted underpinned on the clinical question: How effective is BoNT/A in treating patients with muscle-based (nociceptive) pain disorders?

METHODS

Eligibility Criteria

This study included all possible randomized controlled trials (RCTs) or experimental studies on the effect of botulinum toxin on muscle-based and visceromotor pain. The P.I.C.O.T. framework (population, intervention, comparison, outcome, and timeframe) was used in developing our clinical question, guiding the literature search, and evaluating eligibility of potentially relevant research papers (19).

Included in them were all studies that involved muscle-based and visceromotor pain syndromes, regardless of the respondent's age or sex that involved the use of BONT/A in addressing pain. The comparison was any form of intervention given to the control group (e.g. placebo, usual or standard treatment, etc.). The primary outcome of interest was the pain scores of the study's respondents. No specific timeframe was set for the assessment of pain in the studies that were reviewed. Furthermore, this research did not impose any limitation on the date of publication of research papers. Only papers written in English were included in this study.

Information Sources

This study searched relevant literature in various search engines and research databases, namely: **PubMed, ScienceDirect, EBSCO Host,** and **Google Scholar**. Apart from the literature that was acquired from these searches, we also scrutinized the references of these studies for potentially relevant studies. Additionally, gray literature (defined as reports produced by all levels of government, academics, business, and industry in print and electronic formats but not controlled by commercial publishers) were also included and searched over **ProQuest Dissertations & Theses Database** and **ClinicalTrials.gov**.

Search

We searched relevant literature in the following search engines and research databases: PubMed, ScienceDirect, EBSCO Host, Google Scholar, and ProQuest. An arsenal of search techniques were employed including keyword search, controlled vocabulary or subject heading search, and Boolean logic search. Using keyword search on databases without controlled vocabulary, the following phrases were searched: "botulinum toxin in pain," "botulinum toxin in muscle pain," "muscle-based pain and botulinum toxin," "botulinum toxin in myofascial pain," "botulinum toxin in cervicogenic pain," "botulinum toxin in lumbar pain," "botulinum toxin in neck pain," "botulinum toxin in neuromuscular pain," and "botulinum in nociceptive pain." In contrary, the following Medicine Medical Subject Headings (MeSH) terms were used for databases with controlled vocabulary: "Botulinum toxin" OR "Botulinum Toxin A" OR "Botox" OR "BTX" AND "pain" OR "pain syndromes" OR "nociceptive pain." The search was limited to research on human data and clinical trials. Likewise, reference lists of relevant papers and all selected articles were searched to identify additional trials.

Study Selection

Literature search and eligibility assessment was conducted by two independent reviewers. One reviewer extracted research data and performed quality assessment of the identified articles. The second reviewer, on the other hand, checked the extracted data and performed the quality assessment. Disagreements in judgment between the reviewers were resolved by discussion.

The title, keywords, and abstract of publications identified according to the aforementioned search strategies were independently screened by these reviewers. Inclusion criteria for the title and abstract screening included trials or experimental studies on botulinum toxin on pain (muscle or visceromotor). The same reviewers independently scrutinized full-text researches for final inclusion in the study. The characteristics of included studies are shown in Table 1. In instances of disagreement between the reviewers, these discrepancies were managed through a discussion.

The quality of each selected research article was assessed and rated as either high, moderate, low, or very low quality. In the assessment of risks and biases across the selected research, the Cochrane Collaboration's tool was employed. The following aspects of research were appraised: sequence generation, blinding, allocation concealment, incomplete outcome data, selective outcome reporting, and other sources of bias. Albeit randomized controlled trials or experimental studies will be generally rated as high quality, their quality ranking may be downgraded based on other parameters. The parameters that may decrease the quality of evidence included serious limitations in design, imprecision of results, unexplained heterogeneity, and indirectness of evidence and high probability of publication bias.

Data Collection Process

Data that were extracted from included studies will be carried out by two independent reviewers. An abstraction form was developed and pretested on a number of papers. The abstraction extracted information regarding the authors, publication year, study design, study location, source of funding, duration of study, inclusion criteria, exclusion criteria, duration of pain, type of pain or pain syndrome, participation rate, attrition rate, dose of botulinum toxin administered, outcomes, adverse effects, and results. Disagreements were resolved by discussions between the reviewers. Changes or improvements were the first to be discussed by the reviewers.

Data Items

The variable that was of primary interest in the study was pain or pain syndrome on muscle and visceromotor disorders. We employed the P.I.C.O.T. framework (population, intervention, comparison, outcome, and

Table 1. Characteristics of Trials included in the Analysis (N = 17)

Study (year) and Country	Design	Duration	Participants	Intervention	Outcome	Results
Akiyama et al. (2015) Japan	Randomized-Controlled Trial (RCT)	1 Month	Patients with Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) diagnosed based on the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) criteria	BTX – A, 100 Units	Pain using VAS 0 – 10	Control Group: 6.20 (±2.10) with 16 respondents Experimental Group: 5.10 (±2.00) with 18 respondents
de Boer et al. (2008) The Netherlands	Double-Blind Randomized-Controlled Trial (RCT)	3 Months	Post-stroke patients with spastic hemiplegia, substantial shoulder pain and reduced external rotation of the humerus	BoNT-A, 100 Units	Pain using VAS 0 – 100	Control Group: 46.80 (±27.20) with 10 respondents Experimental Group: 38.10 (±18.20) with 11 respondents
Guarda-Nardini et al. (2012) Italy	Randomized-Controlled Trial (RCT) – Parallel	More than 6 months	Patients with bilateral masticatory muscle pain with or without limited mouth opening range	BTX – Injection (Dysport), 300 Units	Pain using VAS 0 – 10	Control Group: 2.50 (±2.20) with 15 respondents Experimental Group: 24.80 (±2.00) with 15 respondents
Hesse et al. (2011) Germany	Randomized-Controlled Trial (RCT) – Parallel	1 Month	Patients who were first time supratentorial stroke (4–6 weeks after onset); on rehabilitation; partly independent with ADLs; with a Barthel Index >25; non-functional upper extremity with a Fugl-Meyer motor score <20; no volitional wrist or finger extensor activity; with finger and/or wrist flexor stiffness with a Modified Ashworth Scale score (0–5) of 1 or 2.	BTX-A (Xeomin), 150 Units	Pain using a 5-point Ordinal Scale (0 – 4)	Finger Extension: Control Group: 1.80 (±0.70) with 9 respondents Experimental Group: 0.70 (±0.70) with 9 respondents Wrist Extension: Control Group: 2.10 (±0.90) with 9 respondents Experimental Group: 0.90 (±0.80) with 9 respondents
Kasyan et al. (2012) Russia	Randomized-Controlled Trial (RCT)	3 Months	Patients with Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) diagnosed based on on clinical presentation and cystoscopic findings	BTX – A, 100 Units	Pain using VAS 0 – 10	Control Group: 6.40 (±2.80) with 17 respondents Experimental Group: 5.80 (±2.40) with 15 respondents
Kong et al. (2007) Singapore	Randomized-Controlled Trial (RCT)	3 Months	Patients, more than three months post stroke, with hemiplegic shoulder pain associated with shoulder adductor and elbow flexor spasticity	BTX – A, 500 Units	Pain using VAS 0 – 10	Control Group: 4.00 (±1.43) with 9 respondents Experimental Group: 3.00 (±2.00) with 8 respondents

Table 1. Continued

Study (year) and Country	Design	Duration	Participants	Intervention	Outcome	Results
Kuo et al. (2009) Taiwan	Randomized-Controlled Trial (RCT)	3 Months	Patients with Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) diagnosed based on the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) criteria	BoNT-A, 100 Units	Pain using VAS 0 – 10	Control Group: 3.52 (±3.07) with 12 respondents Experimental Group: 2.97 (±1.99) with 29 respondents
Kuo et al. (2009) Taiwan	Randomized-Controlled Trial (RCT)	3 Months	Patients with Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) diagnosed based on the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) criteria	BoNT-A, 200 Units	Pain using VAS 0 – 10	Control Group: 3.52 (±3.07) with 12 respondents Experimental Group: 2.47 (±2.10) with 15 respondents
Kuo et al. (2015) Taiwan	Randomized-Controlled Trial (RCT)	2 Months	Patients with Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) diagnosed based on the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) criteria	BTX – A, 100 Units	Pain using VAS 0 – 10	Control Group: 2.80 (±2.50) with 20 respondents Experimental Group: 2.70 (±2.70) with 40 respondents
Kwanchuay et al. (2015) Thailand	Double-Blind Randomized-Controlled Trial (RCT)	6 Weeks	Patients with myofascial trigger point (MTrP) of the upper trapezius muscle.	BTX – A (Botox), 20 International Units	Pain using VAS 0 – 10	Control Group: 0.5 (±0.7) with 33 respondents Experimental Group: 1.00 (±0.9) with 33 respondents
Lim et al. (2007) South Korea	Double-Blind Randomized-Controlled Trial (RCT)	3 Months	Patients with hemiplegic shoulder pain aged 18 to 78 years	BoNT-A (Botox), 100 Units	Pain using Numeric Rating Scale	Control Group: 5.50 (±1.00) with 11 respondents Experimental Group: 3.20 (±0.50) with 14 respondents
Marco et al. (2007) Spain	Double-Blind Randomized-Controlled Trial (RCT)	6 Months	Post-stroke patients with spastic shoulder pain	BTX – A (Dysport), 500 Units	Pain using VAS 0 – 100	Control Group: 48.30 (±29.40) with 15 respondents Experimental Group: 30.10 (±26.90) with 14 respondents
Nixdorf et al. (2002) Canada	Randomized-Controlled Trial (RCT) – Crossover Technique	More than 6 months	Patients with moderate to severe muscle pain with or without limited opening	BTX – A (Botox), 150 Units	Pain using VAS 0 – 100	Control Group: -1.00 (±16.00) with 10 respondents Experimental Group: -19.00 (±31.00) with 10 respondents

Table 1. Continued

Study (year) and Country	Design	Duration	Participants	Intervention	Outcome	Results
Rosales et al. (2012) Philippines, Hong Kong, Malaysia, Singapore, Thailand	Randomized-Controlled Trial (RCT)	3 Months	Post-stroke patients with impairment using the World Health Organization (WHO) criteria	BoNT-A (Dysport), 500 Units	Pain using VAS 0 – 100	Control Group: 20.72 (±21.53) with 83 respondents Experimental Group: 13.57 (±21.53) with 80 respondents
Shaw et al. (2010) United Kingdom	Multi-center Randomized-Controlled Trial (RCT)	12 Months	Patients with upper limb spasticity due to stroke	BTX – A (Dysport), Maximum of 1,000 Units	Pain using VAS 0 – 10	Control Group: 4.20 (±3.51) with 92 respondents Experimental Group: 2.80 (±3.51) with 97 respondents
Singh et al. (2010) U.S.A.	Randomized-Controlled Trial (RCT)	3 Months	Patients with shoulder pain	BoNT-A	Pain using VAS 0 – 10	Control Group: 5.00 (±4.00) with 162 respondents Experimental Group: 5.00 (±3.50) with 170 respondents
Yelnik et al. (2007) France	Double-Blind Randomized-Controlled Trial (RCT)	1 Month	Post-stroke patients with spastic hemiplegia and shoulder pain	BTX – A (Dysport), 500 Units	Pain using VAS 0 – 10	Control Group: 4.00 (±1.40) with 10 respondents Experimental Group: 1.50 (±2.10) with 10 respondents

timeframe) in developing our clinical questions, guiding our literature searches, and assessing the eligibility of potentially relevant research articles.

Summary Measures

The mean and standard deviation (SD) of pain scores were utilized to calculate the standardized mean difference (Std. MD) and used in the meta-analysis.

Synthesis of Results

This study did not assume one effect size among all the studies that were included. Hence, the overall effect for each meta-analysis was derived using a random-effects model (REM), which takes within-study and between-study variation into account. The mean and SD of the pain scores were utilized to calculate the Std. MD. Statistical heterogeneity between studies were scrutinized using Q statistics test, I^2 statistics, and tau squared (τ^2) statistics.

Additional Analyses

Subgroup analyses based on the dose concentration of BoNT-A and period of follow-up were conducted. Publication bias was evaluated by scrutinizing the Begg's funnel plots (Chouraqui, Dietsch, Musial, & Blehaut, 1995). Formal statistical assessment of funnel plot asymmetry was performed using Egger's regression asymmetry test and Begg's adjusted rank correlation test (Dalgic, Sancar, Bayraktar, Pullu, & Hasim, 2011). All statistical analyses were conducted using the Review Manager (RevMan) version 5.3 and STATA version 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.). A p-value ≤ 0.05 was considered statistically significant.

RESULTS

Study Selection

The literature search retrieved a total of 1,303 articles. After screening these publications, only 61 remaining papers were screened for eligibility. From these articles, 44 were further removed due to the following reasons: (1) 25 articles did not report the mean and standard deviation of the VAS scores; (2) Three studies were case reports and/or case studies;

(3) Two articles were repeated measures study without a comparison; and (4) Nine studies were qualitative studies. As presented in Figure 1, a total of 17 articles were included in the meta-analytic study.

Study Characteristics

All studies selected for this review were RCTs with a total of 17 research papers. Table 1 presents a summary of characteristics of the included studies.

Results of Individual Studies

The summary of results of each of these studies included is presented in Table 1.

Synthesis of Results

It can be gleaned in Figure 2 that the analysis of the pooled data showed a significant difference in the mean pain scores between the utilization of BoNT/A and the counterfactual condition using the random-effects model ($z = 2.94$, $p = 0.003$, 95%CI = –0.67, –0.13). It is also worth noting that a significantly ($\chi^2 = 66.56$, $p<0.00001$) large heterogeneity ($I^2 = 74\%$; $\tau^2 = 0.21$) was noted in the trials included.

DISCUSSION

Pooled data analysis illustrated that there is a significant difference between the muscle-based and visceromotor pain scores with lower pain scores in the BoNT/A group. This result may be attributed to

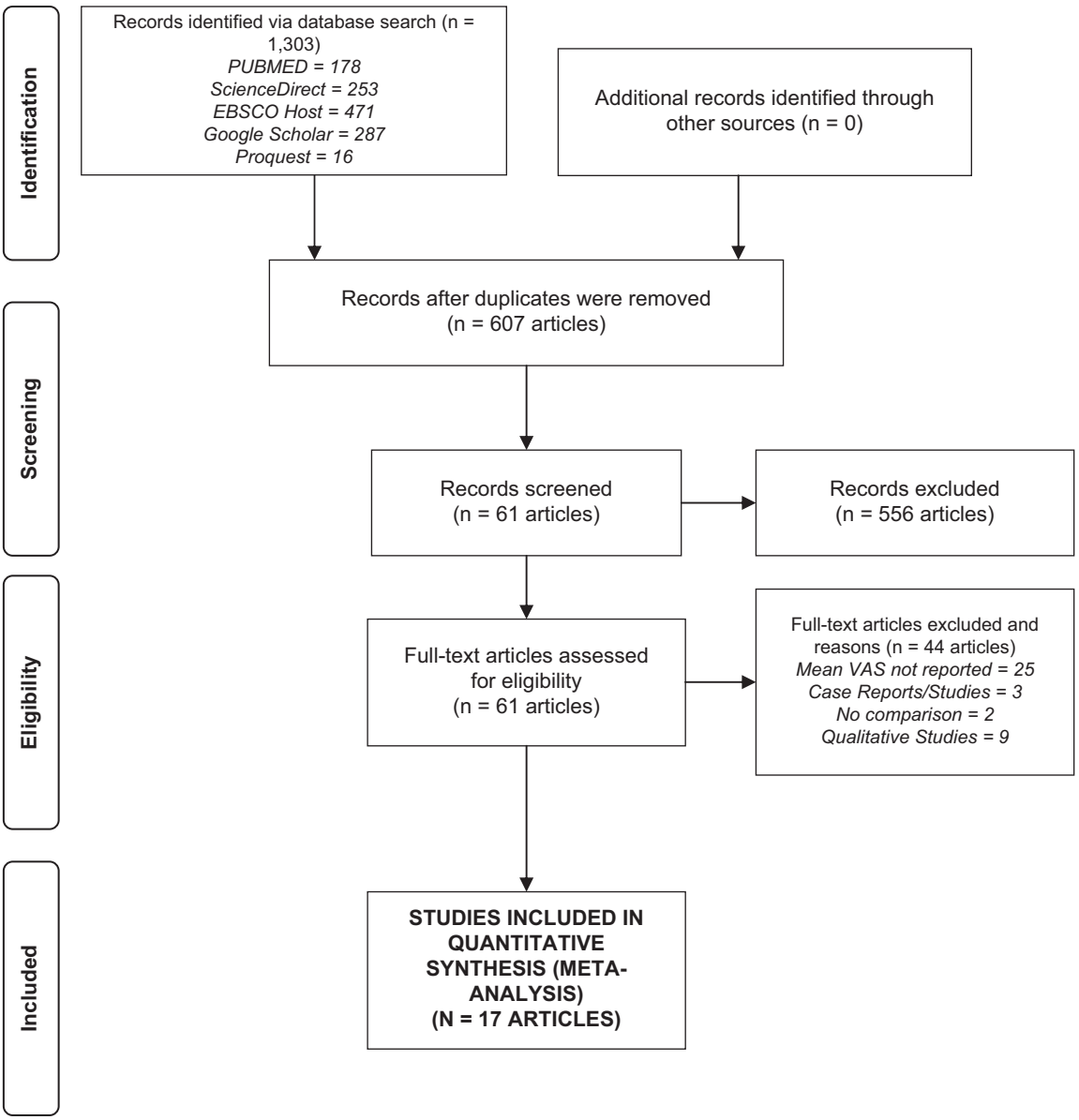

Figure 1. PRISMA Flow Diagram of Study Selection.

Study or Subgroup	Botox Mean	Botox SD	Botox Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Akiyama et al. (2015)	5.1	2	18	6.2	2.1	16	5.7%	-0.52 [-1.21, 0.16]
de Boer et al. (2008)	38.1	18.2	11	46.8	27.2	10	4.6%	-0.36 [-1.23, 0.50]
Guarda-Nardini et al. (2012)	4.8	2	15	2.5	2.2	15	5.2%	1.06 [0.29, 1.84]
Hesse at al. (2011) F Extensor	0.7	0.7	9	1.8	0.7	9	3.7%	-1.50 [-2.57, -0.42]
Hesse at al. (2011) W Extension	0.9	0.8	9	2.1	0.9	9	3.8%	-1.34 [-2.39, 0.29]
Kasyan et al. (2012)	5.8	2.4	15	6.4	2.8	17	5.6%	-0.22 [-0.92, 0.47]
Kong et al. (2007)	3	1.79	8	4	1.43	9	4.1%	-0.59 [-1.57, 0.39]
Kuo et al. (2009) 100 U	2.97	1.99	29	3.52	3.07	23	6.5%	-0.21 [-0.76, 0.33]
Kuo et al. (2009) 200 U	2.47	2.1	15	3.52	3.07	23	5.8%	-0.38 [-1.03, 0.28]
Kuo et al. (2015)	2.7	2.7	40	2.8	2.5	20	6.6%	-0.04 [-0.57, 0.50]
Kwanchuay et al. (2015)	1	0.9	33	0.5	0.7	33	6.9%	0.61 [0.12, 1.11]
Lim et al. (2007)	3.2	0.5	14	5.5	1	11	3.3%	-2.93 [-4.12, -1.74]
Marco et al. (2007)	30.1	26.9	14	48.3	29.4	15	5.3%	-0.63 [-1.38, 0.12]
Nixdorf et al. (2002)	-19	31	10	-1	16	10	4.4%	-0.70 [-1.61, 0.21]
Rosales et al. (2012)	13.57	21.525	80	20.72	21.525	83	8.0%	-0.33 [-0.64, -0.02]
Shaw et al. (2010)	2.8	3.5059	97	4.2	3.5059	92	8.1%	-0.40 [-0.69, -0.11]
Singh et al. (2010)	5	3.5	170	5	4	162	8.5%	0.00 [-0.22, 0.22]
Yelnik et al. (2007)	1.5	2.0969	10	4	1.3979	10	4.0%	-1.34 [-2.34, -0.35]
Total (95% CI)			597			567	100.0%	-0.40 [-0.67, -0.13]

Heterogeneity Tau^2 = 0.21; Chi^2 = 66.56, df = 17 (P < 0.00001); I^2 = 74%
Test for overall effect: Z = 2.94 (P = 0.003)

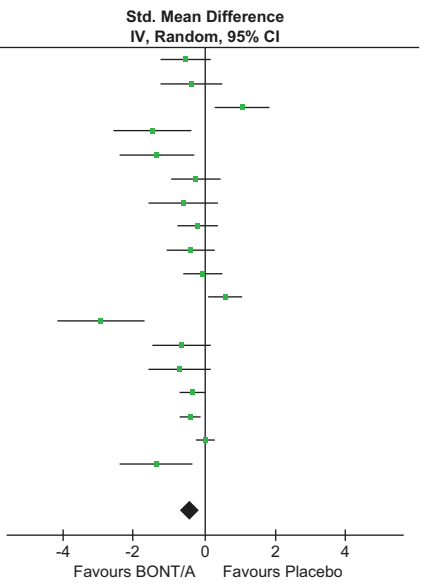

Figure 2. Subgroup Analysis of Pain Scores Between Botulinum Toxin A and Placebo According to Dose Concentration.

the pathophysiological mechanism of BoNT/A that involves the blockade of acetylcholine (Ach) neurotransmitter release from the presynaptic nerve at the neuromuscular junction (18,27). As a result of such an action, muscle contraction is halted and leads to muscle relaxation. The current finding may also be explained by the biological response of the body with BoNT/A. The analgesic effect of BoNT may be due to the inhibition of the release of local neuropeptide substances such as substance P, calcitonin gene-related peptide (CGRP), glutamate, and transient receptor potential vanilloid 1 (TRP1), all of which mediate actions on the neuromuscular junctions and muscle fibers of the body (27). This effect, alongside the immediate relaxation of muscles leads to lower pain-inducing substances (e.g. prostaglandins) and thus lower pain scores.

Nonetheless, the large heterogeneity indicates that approximately 74% of the total variability was caused by the difference in the true effect sizes or between-study variance and only 26% was due to sampling error or within-study variance. Although the variation between each study was already accounted by using REM and were attempted to be explained using subgroup analyses according to dose concentration and length of follow-up periods, the variability was still significantly large and may affect the estimated pooled values. In response, future studies must attempt more exhaustive search techniques to increase the sample size of clinical trials that will be included in future meta-analytic studies, thus identifying other possible sources of heterogeneity that can be considered.

CONCLUSION

This study determined the effectiveness of BoNT-A in treating muscle-based (nociceptive) and visceromotor pain disorders. Employing REM, results showed a significant difference in the standardized mean pain scores of the two treatment approaches favoring the BoNT-A group denoting its effectiveness in decreasing nociceptive and visceromotor pain scores.

The researchers recognized the limitations of the study which included a small sample size of studies that accounted for the high heterogeneity. Further, although included in the search plan and technique, there was no unpublished study (e.g. institutional papers, theses, or dissertations) retrieved to date. Finally, subgroup analysis was only conducted on two stratifications: dose concentration and period of follow-up.

Disclosure and Conflict of Interest

This research has no disclosure of interest to report.

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