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Efficacy and Safety of Intra-Articular Botulinum Toxin A Injection for Knee Osteoarthritis

A Systematic Review, Meta-Analysis, and Meta-Regression of Clinical Trials

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Background: Botulinum toxin A has the potential to be used for analgesia because of its anti-inflammatory effect. The utility of intra-articular injections of botulinum toxin A for knee osteoarthritis remains unclear. The aim of this study was to analyze the utility of such injections in knees with osteoarthritis.

Methods: We conducted a literature search of 4 databases (Scopus, PubMed, ClinicalTrials.gov, and Europe PMC) up to September 10, 2022, using formulated keywords. Articles were included in the study if they had data on botulinum toxin A injection compared with the control group in patients with osteoarthritis of the knee. Results were summarized using the standardized mean difference (SMD) and accompanying 95% confidence interval (CI).

Results: Pooled analysis of data from 6 trials involving 446 patients with knee osteoarthritis revealed that, compared with placebo, intra-articular injection of botulinum toxin A was associated with greater reductions in early visual analog scale (VAS) pain (SMD, −0.63 [95% CI, −1.08 to −0.18], p = 0.007, I^2 = 79%), late VAS pain (SMD, −0.57 [95% CI, −1.07 to −0.08], p = 0.02, I^2 = 81%), early Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (SMD, −0.84 [95% CI, −1.61 to −0.06], p = 0.03, I^2 = 90%), and late WOMAC (SMD, −1.12 [95% CI, −1.91 to −0.32], p = 0.006, I^2 = 93%) scores from baseline in patients with knee osteoarthritis.

Conclusions: Intra-articular injection of botulinum toxin A may offer benefits in reducing pain and improving function in patients with knee osteoarthritis, with a relatively good safety profile. Larger randomized trials are warranted to confirm the results of our study.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

Osteoarthritis (OA) is a chronic degenerative joint disease that is commonly encountered in daily practice in older individuals and causes prolonged pain, decreased function, and disability[1]. In 2015, the World Health Organization estimated that 9.6% of men and 18% of women >60 years old around the world had symptomatic OA[2]. The prevalence of OA is predicted to reach 25% of the world population in 2040, resulting in a prominent socioeconomic burden in the next few decades[3].

Also known as degenerative arthritis, this multifactorial disease is characterized by progressive joint degradation leading to permanent cartilage damage, subchondral bone sclerosis, and synovial inflammation[4]. The knees, which are the largest synovial joints in the human body, account for almost four-fifths of the total burden of OA worldwide, and the prevalence of knee OA increases with increasing patient obesity and age[5]. The pathological process in knee OA that results in pain, stiffness, and mobility limitations involves structural changes in and around the knee joint, especially cartilage damage and osteophyte formation, that affect knee function and result in inflammatory symptoms[6].

Several modalities for treating knee OA are available, beginning with conservative management (e.g., physical exercise and weight control) and pharmacological treatment (e.g., acetaminophen) and ending with total knee replacement[7]. Historically, cyclooxygenase inhibitors such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) have been the drugs most frequently used for OA. However, long-term use of these drugs can result in gastrointestinal, renal, cardiovascular, and hematological adverse events[8]. If a patient does not respond to oral medications, then intra-articular injections may be considered[9]. It is hypothesized that topical treatment will result in fewer systemic adverse events, and injecting the drugs directly into the joint is

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expected to produce an immediate effect on the joint[9]. Intra-articular administration of several agents has been studied, and intra-articular therapy was often more effective than NSAIDs and other systemic pharmacological agents[10]. Initially, intra-articular injection of corticosteroids was introduced as an alternative to systemic administration. More recently, intra-articular viscosupplementation with hyaluronic acid and regenerative treatments were introduced[10].

Although initially intended to be used as a treatment for strabismus, botulinum toxin A is now widely used for various purposes, and in-depth research has been performed[11]. Botulinum toxin A can cause muscle paralysis by inhibiting the production of acetylcholine at the neuromuscular junction[11]. Inhibitory effects on neuropeptide secretion and suppression of inflammation by botulinum toxin A have also been shown to possibly produce an analgesic effect in several studies[12]. Previous meta-analyses published in 2017 and 2018 demonstrated that intra-articular injections of botulinum toxin A may improve pain and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores better than placebo in adult patients with refractory joint pain[13,14]. However, the evidence regarding the efficacy and safety of intra-articular botulinum toxin A injections for knee OA remains unclear. The aim of the present systematic review and meta-analysis was therefore to perform an up-to-date evaluation of the efficacy and safety of botulinum toxin A for the management of knee OA.

Materials and Methods

Eligibility Criteria

The inclusion criteria for this study, reported on the basis of the PICOS formulation, were as follows. Participants: patients diagnosed with knee OA of any grade. Intervention: intra-articular injection at the knee joint using a 100 to 200-IU dose of botulinum toxin A. Comparison: injections containing placebo such as 0.9% saline solution or education only without any injections. Outcomes: reductions (from baseline) in early visual analog scale (VAS) pain (at ≤4 weeks), late VAS pain (at >4 weeks), early WOMAC (at ≤4 weeks), and late WOMAC scores (at >4 weeks), and any adverse events resulting from the intervention. Studies: randomized clinical trials.

The following were exclusion criteria: (1) studies of children (<18 years old); (2) studies of pregnant women; (3) studies without a control or comparison group; (4) observational (cohort, case-control, cross-sectional) studies, case series, and case reports; (5) non-primary studies (review articles, correspondence, editorials); and (6) studies not available in the English language.

Literature Search and Study Selection

Four databases (Europe PMC [PubMed Central], Scopus, PubMed, and ClinicalTrials.gov) were searched for English-language articles until September 10, 2022, with the following keywords: "(knee osteoarthritis OR OA knee OR gonarthrosis OR genu osteoarthritis OR OA genu) AND (botulinum toxin OR botox OR BTX OR BoNT OR dysport) AND (clinical trials OR randomized trials OR RCT)." Additional details regarding the search strategies used with each study database are shown in Appendix Supplementary Table 1. Screening of titles and abstracts was carried out independently by 2 reviewers to identify eligible studies. The reference lists of the eligible studies were also evaluated for additional potentially relevant articles. All duplicates were removed. The same 2 reviewers then evaluated the remaining full-text articles for eligibility on the basis of the inclusion and exclusion criteria; any discrepancies were resolved through discussion. The results were compiled in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline[15].

Data Extraction

Two reviewers extracted the author names, year of publication, study design, outcomes of interest, and the following sample characteristics: sample size, age, gender, body mass index (BMI), Kellgren-Lawrence grade, and dose of botulinum toxin.

The following outcomes of interest were analyzed: reductions (from baseline) in early and late VAS pain and WOMAC scores, and any adverse events resulting from the intervention. Early and late time intervals were defined as ≤4 and >4 weeks after surgery, respectively. The early reduction was thus defined as the score reported up to 4 weeks after the injection minus the score at baseline, and the late reduction was defined as the score at >4 weeks minus the baseline score. A VAS with a score ranging from 0 (no pain) to 10 (unbearable pain) has been shown to be a valid and reliable measure for pain[16]. The WOMAC index is a disease-specific, self-administered instrument for patients with OA of the knee or hip[17]. The score has 3 dimensions (with a total of 24 individual scenarios) that measure pain (5 scenarios), stiffness (2 scenarios), and physical function (17 scenarios). These results are scored on scales of 0 to 20 for pain, 0 to 8 for stiffness, and 0 to 68 for physical function. A higher score on a scale indicates greater pain, stiffness, or physical dysfunction.

Risk-of-Bias Assessment

Two reviewers assessed the risk of bias in each included clinical trial using the Risk of Bias version 2 (RoB v2) tool from the Cochrane Collaboration[11,18]. This tool assesses 5 domains: the randomization process, deviations from the intended intervention, missing outcome data, measurement of the outcomes, and selection of the reported results. The results for these 5 domains classify the risk of bias in a randomized clinical trial (RCT) as low if all domains are rated as having a low risk of bias, as having some concern if ≥1 domains have some concern regarding bias, and as high if ≥1 domains have a high risk of bias[11,18].

Statistical Analysis

Outcomes consisting of continuous variables were analyzed using the inverse-variance method to obtain the standardized mean difference (SMD) and accompanying 95% confidence interval (CI). Random-effect modeling was used, as heterogeneity due to differences in the botulinum toxin dose and in the OA grading among the included studies was expected. Heterogeneity was assessed using the I^2 (inconsistency) value; ≤25%,

26% to 50%, and >50% were categorized as low, moderate, and high heterogeneity, respectively[11]. Data that had been reported as the median and interquartile range or as the median, minimum, and maximum were converted to the mean and standard deviation (SD) using the formula from Wan et al.[19]. Meta-regression with a random-effect model using the restricted maximum likelihood was performed for age, gender, BMI, and Kellgren-Lawrence grade to assess the effect of the interaction between botulinum toxin A injection and each of these prespecified variables on the outcomes of interest. Funnel plots were utilized to provide a qualitative assessment of the risk of publication bias.

Source of Funding

This study did not receive any external funding.

Results

Study Selection and Characteristics

A total of 537 studies were found in the PubMed, Scopus, Europe PMC, and ClinicalTrials.gov databases. After removing duplicates and screening on the basis of the titles and abstracts, 517 articles were eliminated, and the remaining 20 articles underwent full-text review to assess their eligibility. Fourteen of the 20 articles were eliminated because the population was not specifically patients with knee OA (5 articles), other well-known therapeutic agents such as corticosteroids or hyaluronic acid were used in the comparison group (5 articles), the study did not have a control group (1 article), or the study was not an RCT (3 articles). The remaining 6 studies[20-25], with a total of 446 patients with knee OA, were analyzed (Fig. 1). Of these 6 RCTs, 3 had a double-blinded design, 2 had a single-blinded design, and the remaining article did not provide sufficient information to determine whether it was a single-blinded or open-label (unblinded) RCT. The number of participants in the included studies ranged from 40 to 132. Most of the participants in the included studies had Kellgren-Lawrence grade-II or III knee OA. All of the included studies used 100 to 200 IU of botulinum toxin A injected intra-articularly into the knee joint, usually with ultrasound guidance. Details regarding the characteristics of each included study are shown in Table I.

Study Quality

The RoB v2 tool categorized 4 of the 6 included trials as having a low risk of bias in all 5 domains. The remaining 2 trials had some concerns regarding the risk of bias because the outcome measurement information was not clear enough to establish that it was collected in a blinded fashion and thus free from the possibility of manipulation (Table II).

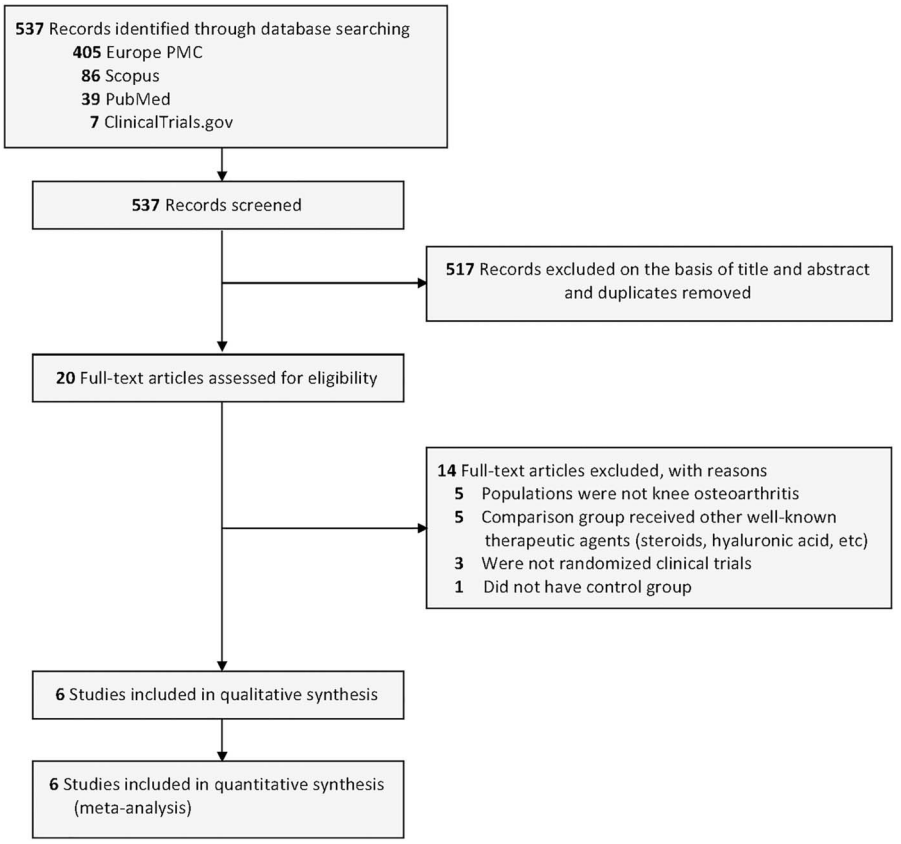

Fig. 1

PRISMA diagram showing the selection of studies for inclusion in the systematic review and meta-analysis.

TABLE I Characteristic of the Included Studies*

Study	Design	Population					Intervention	Comparison
		Sample Size	Age† *(yr)*	Male	BMI† *(kg/m²)*	Kellgren–Lawrence Grade		
Arendt-Nielsen[20] (2017)	Double-blinded RCT	121	62.3 ± 8.6	48.7%	28 ± 3.9	9.1% I, 62% II, 28.9% III	200 IU botulinum toxin A, single dose into patellofemoral space using ultrasound guidance	Placebo (2 mL of 0.9% saline solution)
Bao[21] (2018)	Single-blinded RCT	40	65.8 ± 3.5	47.5%	NA	65% II, 32.5% III, 2.5% IV	100 IU botulinum toxin A, single dose into suprapatellar bursa using ultrasound guidance	Placebo (2.5 mL of 0.9% saline solution)
Hsieh[22] (2016)	Prospective RCT	41	67.9 ± 6.8	39%	27.4 ± 3.7	2.4% I, 29.3% II, 63.4% III, 4.9% IV	100 IU botulinum toxin A, single dose at junction of upper one-third and lower two-thirds of patella without ultrasound guidance	Education only
Mahowald[23] (2009)	Single-blinded RCT	42	NA	NA	NA	NA	100 IU botulinum toxin A + lidocaine, single dose	Placebo (saline solution + lidocaine)
McAlindon[24] (2018)	Double-blinded RCT	132	60.8 ± 7.9	41.6%	31 ± 6.1	56% II, 44% III	200 IU botulinum toxin A, single dose injected intra-articularly using ultrasound guidance	Placebo (2 mL of 0.9% saline solution)
Mendes[25] (2019)	Double-blinded RCT	70	63.5 ± 6.7	7.1%	30.4 ± 5	55.7% II, 44.3% III	100 IU botulinum toxin A, single dose 2 cm from superolateral angle of patella	Placebo (2 mL of 0.9% saline solution)

*BMI = body mass index, RCT = randomized clinical trial, NA = not available. †The values are given as the mean ± standard deviation.

TABLE II Risk-of-Bias Assessment of the Included Studies*

Study	Randomization Process	Deviations from Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall
Arendt-Nielsen[20] (2017)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Bao[21] (2018)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Hsieh[22] (2016)	Low risk	Low risk	Low risk	Some concerns	Low risk	Some concerns
Mahowald[23] (2009)	Low risk	Low risk	Low risk	Some concerns	Low risk	Some concerns
McAlindon[24] (2018)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Mendes[25] (2019)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

*Using the RoB v2 tool.

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Botulinum Toxin Versus Control

Reduction in Early VAS Pain

Six studies (n = 446 patients with knee OA) reported on early VAS pain. The pooled analysis showed that intra-articular injection of botulinum toxin A was associated with a greater reduction in the VAS pain score from baseline to ≤4 weeks postoperatively than in the control group (SMD, −0.63 [95% CI, −1.08 to −0.18], p = 0.007, I^2 = 79%, random-effect modeling) (Fig. 2-A).

Reduction in Late VAS Pain

Five studies (n = 404 patients with knee OA) reported on late VAS pain. The pooled analysis showed that intra-articular botulinum toxin A injection was associated with a greater reduction in the VAS pain score from baseline to >4 weeks postoperatively than in the control group (SMD, −0.57 [95% CI, −1.07 to −0.08], p = 0.02, I^2 = 81%, random-effect modeling) (Fig. 2-B).

Reduction in Early WOMAC

Five studies (n = 325 patients with knee OA) reported on the early WOMAC score. The pooled analysis showed that intra-articular botulinum toxin A injection was associated with a greater reduction in the WOMAC score from baseline to ≤4 weeks postoperatively than in the placebo group (SMD, −0.84 [95% CI, −1.61 to −0.06], p = 0.03, I^2 = 90%, random-effect modeling) (Fig. 2-C).

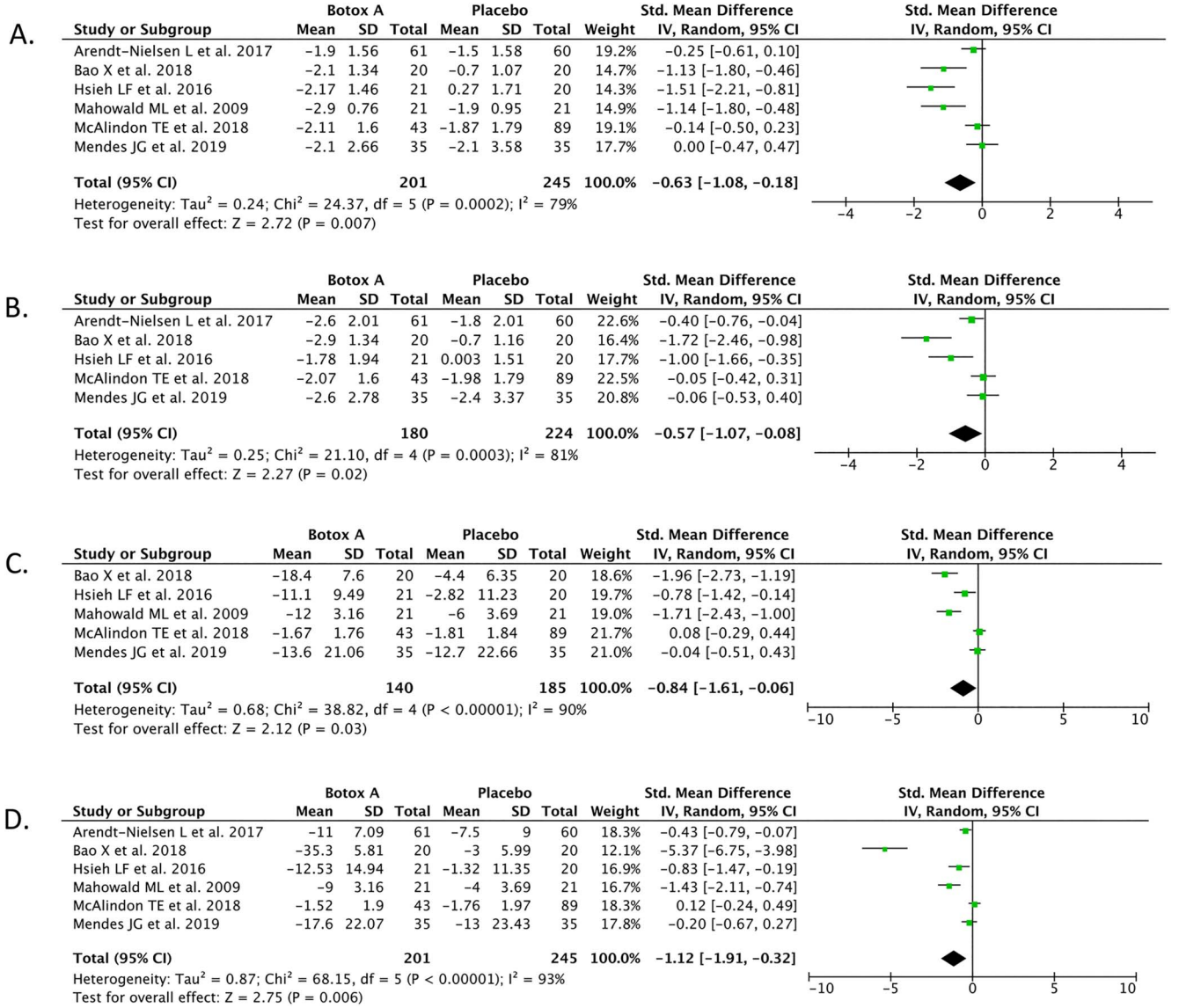

Fig. 2

Forest plots showing the comparison between intra-articular injection of botulinum toxin A (Botox A) and placebo in patients with knee OA: reduction in VAS pain scores at early time points (**Fig. 2-A**), reduction in VAS pain scores at late time points (**Fig. 2-B**), reduction in WOMAC scores at early time points (**Fig. 2-C**), and reduction in WOMAC scores at late time points (**Fig. 2-D**). df = degrees of freedom and IV = inverse variance.

Reduction in Late WOMAC

Six studies (n = 446 patients with knee OA) reported on the late WOMAC score. The pooled analysis showed that intra-articular botulinum toxin A injection was associated with a greater reduction in the WOMAC score from baseline to >4 weeks postoperatively than in the control group (SMD, − 1.12 [95% CI, − 1.91 to − 0.32], p = 0.006, I^2 = 93%, random-effect modeling) (Fig. 2-D).

Adverse Events

Four of the 6 studies reported safety outcomes for intra-articular botulinum toxin A injection. In 1 study[24], the most commonly reported adverse events were arthralgia (20.9%), joint swelling (9.3%), hypertension (7%), and nasopharyngitis (4.7%); however, there were no significant differences in these adverse events compared with the control group. The remaining 3 studies[20,23,25] reported no adverse events associated with the intra-articular botulinum toxin A injection.

Meta-Regression

Meta-regression was used to identify factors that influenced the relationship between intra-articular botulinum toxin A injection and each outcome of interest. Variability in those outcomes in patients with knee OA receiving botulinum toxin A treatment can be explained by patient factors that are known to be predictors of the outcomes of treatment (see Appendix Supplementary Table 2). The meta-regression analysis revealed that the association between intra-articular botulinum toxin A injection and the reduction in the VAS pain score at ≤4 weeks in patients with knee OA was significantly influenced by age (beta coefficient = −0.2046 [95% CI, −0.3332 to −0.0760], p = 0.0018) (see Appendix Supplementary Fig.1-A) but was not influenced by gender (p = 0.4383), BMI (p = 0.1382), or Kellgren-Lawrence grade (p = 0.2267) (see Appendix SupplementaryFigs. 1-B, 1-C, and 1-D). The reduction in the VAS pain score at >4 weeks was also significantly influenced by age (beta = −0.1858 [95% CI, −0.3570 to −0.0145], p = 0.0335) (see Appendix Supplementary Fig. 2-A) and BMI (beta = 0.1759 [95% CI, 0.0321 to 0.3196], p = 0.0165) (see Appendix Supplementary Fig. 2-B) but not by gender (p = 0.3584) or Kellgren-Lawrence grade (p = 0.9226) (see Appendix Supplementary Figs. 2-C and 2-D).

The meta-regression analysis also revealed that the association between intra-articular botulinum toxin A injection and the reduction in the WOMAC score at ≤4 weeks was not significantly influenced by age (p = 0.2186), gender (p = 0.3442), or Kellgren-Lawrence grade (p = 0.7861) in patients with knee OA (see Appendix Supplementary Figs. 3-A, 3-B, and 3-C). The influence of BMI on this outcome of interest could not be analyzed because of insufficient data in the included studies. The reduction in the WOMAC score at >4 weeks was significantly influenced by BMI (beta = 0.1968 [95% CI, 0.0534 to 0.3401], p = 0.0071) (see Appendix Supplementary Fig. 4-A) but not by age (p = 0.3522), gender (p = 0.4919), or Kellgren-Lawrence grade (p = 0.5332) (see Appendix Supplementary Figs. 4-B, 4-C, and 4-D).

Publication Bias

Because publication bias in reviews of ≤10 studies is hampered by the resulting lack of power, making the results less reliable[26,27], it was not assessed in the current analysis of 6 studies.

Discussion

The pooled analyses in this study revealed that intra-articular injection of botulinum toxin A (at a dose of 100 to 200 IU) was associated with greater reductions, compared with the control group, in the VAS pain score at ≤4 weeks, VAS pain score at >4 weeks, WOMAC score at ≤4 weeks, and WOMAC score at >4 weeks in patients with knee OA. The relationships of intra-articular botulinum toxin A injection with reductions in VAS pain scores at early and late time points were significantly influenced by age, and the latter was also influenced by BMI. The meta-regression analysis indicated that BMI significantly influenced the relationship between botulinum toxin A injection and the reduction in the WOMAC score at late time points. In addition to its effectiveness in improving pain, intra-articular administration of botulinum toxin A in patients with knee OA was also relatively safe; no serious adverse events or mortality were reported.

Numerous recent studies have indicated that OA has an inflammatory component, rather than being simply a non-inflammatory degenerative joint disease[28,29]. Inflammatory cytokines, such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α, chemokines, and other inflammatory mediators produced by the synovium and chondrocytes can be detected in the synovial fluid of patients with OA[28,29]. Joint structures contain Aδ, Aβ, and C nerve fibers whose excitation threshold becomes lower in cases of injury and inflammation. Aδ fibers may be sensitized by TNF-α, while C fibers may be sensitized by TNF-α, IL-6, IL-1β, or IL-17A, in response to innocuous or noxious mechanical stimuli[30,31]. Neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) also play an important role in pain generation at locations outside the spine through sensitization of nerves and nociceptors (peripheral sensitization)[32]. Chronic joint inflammation is also associated with hyperexcitability of spinal nociceptive neurons (central sensitization)[33,34].

Botulinum toxin A may counteract and inhibit these peripheral and central sensitization processes, thereby modulating the pain resulting from OA. Release of substance P from dorsal-root ganglion neurons and stimulated release of CGRP from trigeminal ganglion neurons have been shown to be inhibited by the administration of botulinum toxin A[35,36]. Studies have also shown that botulinum toxin A may reduce the expression of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, dampening the inflammatory process and reducing pain propagation resulting from peripheral stimuli[35,37,38]. These reductions in peripheral sensitization and afferent input to the spinal cord from peripheral nerve endings may indirectly decrease the central sensitization process. Botulinum toxin A may also be transported along the axon in a retrograde manner and modulate neuronal activity in the central nervous system

through stimulation of inhibitory gamma-amino butyric acid (GABA)-A receptors and μ opioid receptors in the spinal cord[12,39,40]. All of these properties of botulinum toxin A may explain why administration of this toxin is able to reduce pain in patients with knee OA.

This study has several limitations. First, available data regarding botulinum toxin injection for the management of knee OA are limited, and our results are therefore based on a relatively small number of clinical trials. Second, notable heterogeneity was seen in some of the outcomes of interest in the study, which can have resulted from differences in the botulinum toxin A dosage and in the proportions of Kellgren-Lawrence grades of knee OA. Third, several of the clinical trials included in this study have some concern regarding bias, primarily because of a lack of blinding during measurement of the outcomes. Finally, the total cost of using intra-articular botulinum toxin A injection for knee OA could not be analyzed because cost data were lacking in the included studies. The high cost of botulinum toxin injection[11] is a major concern regarding this potential treatment for knee OA.

In conclusion, this systematic review and meta-analysis suggests that intra-articular injection of botulinum toxin A may improve OA symptoms better than placebo does in patients with knee OA, as evidenced by greater reductions in both the VAS pain and WOMAC scores. Larger, well-conducted RCTs are warranted to confirm the results of this study.

Appendix

eA Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJSOA/A461). ■

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