Intra-Articular Botulinum Toxin in Osteoarthritis Treatment: A Systematic Review

Toxina Botulínica Intra-Articular no Tratamento da Osteoartrose: Uma Revisão Sistemática

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Resumo

Introdução: O objetivo do estudo foi analisar a literatura atual relativamente aos efeitos da aplicação intra-articular (IA) de toxina botulínica (BoNT) no tratamento da osteoartrose (OA), no que diz respeito ao controlo da dor e à otimização funcional.

Métodos: Foi realizada uma pesquisa abrangente nas bases de dados PubMed, Cochrane Central Register of Controlled Trials (CENTRAL) e Scopus até outubro de 2023, de acordo com as diretrizes PRISMA. As palavras-chave foram: "Injeções intra-articulares" AND "Toxinas botulínicas" AND "Osteoartrose". Os critérios de inclusão foram: i) estudos elaborados em seres humanos; ii) estudos elaborados em seres humanos com diagnóstico clínico de osteoartrose de alguma articulação; iii) estudos que utilizaram a toxina botulínica tipo A; iv) estudos que aplicaram a BoNT em alguma articulação. Os critérios de exclusão foram: i) artigos de revisão; ii) períodos de *follow-up* inferiores a um mês. Dois revisores independentes foram responsáveis pela seleção e extração dos dados de cada estudo.

Resultados: Trezentos e vinte e oito estudos foram obtidos e dezanove artigos preencheram os critérios de inclusão definidos. Os estudos compararam IA BoNT com placebo e outros tratamentos para a OA nas articulações temporomandibulares, dos ombros, joelhos e tornozelos.

Conclusão: Os resultados parecem revelar que a IA BoNT pode trazer benefícios clínicos de curto e longo prazo no controlo da dor e na mobilidade em doentes com OA de várias articulações. No entanto, mais ensaios clínicos randomizados (ECR) devem ser realizados para determinar as doses mais eficazes para a administração de IA BoNT em cada articulação.

Palavras-chave: Injecções Intra-Articulares; Osteoartrite/tratamento; Toxinas Botulínicas/uso terapêutico; Toxinas Botulínicas Tipo A/uso terapêutico.

Abstract

Introduction: The study aimed to analyze current evidence regarding the effects of intra-articular (IA) Botulinum Toxin (BoNT) application in Osteoarthritis (OA) treatment on pain management and functional improvement.

Methods: A comprehensive search of PubMed, Cochrane Central Register of Controlled Trials (CENTRAL) and Scopus databases from inception until October 2023 was performed according to PRISMA guidelines. The keywords were: "Injections, Intra-articular" AND "Botulinum toxins" AND "Osteoarthritis". The inclusion criteria were: i) studies made with human study groups; ii) studies made in people with a diagnosis of osteoarthritis of any joint; iii) studies that used botulinum toxin type A; iv) studies that applied intra-articular

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BoNT in a joint. The exclusion criteria were: i) review articles; ii) follow-up periods with less than a month. Two independent reviewers were responsible for the selection and data extraction from each study.

Results: Three hundred and twenty-eight studies were reviewed and nineteen articles met the inclusion criteria. The studies compared IA BoNT to placebo and other OA treatments in temporomandibular, shoulder, knee and ankle joints.

Conclusion: Results reveal that IA BoNT can have short and long-term clinical benefits in pain control and mobility in patients with OA. However, more Randomized Clinical Trials (RCTs) should be performed to determine the effective dosages to administer IA BoNT for each joint.

Keywords: Botulinum Toxins/therapeutic use; Botulinum Toxins, Type A/therapeutic use; Injections, Intra-Articular; Osteoarthritis/drug therapy.

Introduction

Osteoarthritis (OA) is a widespread musculoskeletal disease and a leading cause of chronic disability and up to 240 million people worldwide suffer from it.[1,2] Overall, quality of life (QOL) is significantly affected by OA in multiple domains that involve physical functioning, however adverse effects on mental health have been noted as well.[1]

OA is associated to chronic inflammation and persistent oxidative stress that promotes continuous joint degeneration and cartilage destruction, which can result in joint space narrowing, osteophyte formation, sclerosis, irregularity of the cortical joint surface and sub-cortical cyst formation.[2]

OA can affect every joint in the human body, although it is most common in knee, hip, distal and proximal interphalangeal joints, first trapeziometacarpal joint, the first metatarsophalangeal joint and the facet joints of the spine. Other joints, such as the elbow, wrist, shoulder, and ankle are less commonly affected.[3]

OA is primarily a clinical diagnosis. Plain radiographies can be helpful to confirm the diagnosis and exclude other pathologies. However, other imagiologic tests, such as computed topographies or magnetic resonance imaging (MRI), are rarely needed.[3] Risk factors for OA development include genetics, female sex, advancing age, diet and obesity. However, injury, joint malalignment and abnormal loading of the joints can also contribute to the degeneration of joint cartilage.[4]

The most prominent symptom of patients with OA is pain. Early in the course of the disease, pain is predictable and caused by specific activities. Over time, pain and other joint symptoms become less predictable and more constant, with daily activities beginning to become affected. In advanced stages, constant dull and aching pain is accompanied by unpredictable, intense, severe pain, which leads to avoidance of certain activities.[3] Other non-pain symptoms of OA are swelling, clicking, locking, grating, crepitus, cramping, reduced range of motion (ROM), and deformity.[3]

There is no cure for OA. Current treatment follows a stepwise approach with reduction of modifiable risk factors, physical modalities and pain control management with oral analgesics or intra-articular therapies.[4,5] Non-steroid anti-inflammatory drugs (NSAIDs) are usually used to control pain in the initial stages of the disease, however, there are safety concerns that limit the use of NSAIDs for long-term pain management, which means there is a need for a secure, well-tolerated and effective long-term treatment for patients with OA that are not suitable for a surgical approach.[5]

Botulinum toxin (BoNT) is a multi-molecular complex toxin produced by anaerobic strains of *Clostridium botulinum*. This substance is associated with complex proteins that protect them from degradation.[6] Some studies suggest that intra-articular administration of BoNT type A (BoNT-A) may inhibit neuropeptide and inflammatory mediators release from the nociceptors, reducing the intensity of pain that arises from neurogenic inflammation related to OA.[6] BoNT seems to be able to provide satisfactory short-term outcomes in patients with pain sensitization by modulating neurotransmitter release, peripheral nociceptive transduction and chronic pain from central sensitization.[5] Thereby, it may be a suitable option for long-term pain control management in OA patients who are refractory to other treatments.

The aim of this study is to systematic review the current evidence related to the effects of intra-articular BoNT application in OA management of different joints, regarding pain management and functional improvement.

Methods

Literature Research

A thorough systematic review of the current literature was performed, according to PRISMA statement guidelines. The keywords applied were: “Injections, Intra-articular” AND “Botulinum toxins” AND “Osteoarthritis”. The research was performed in October 2023 and no language or time restrictions were applied. The inclusion criteria were: i) studies made with human study groups; ii) studies made in people with a diagnosis of osteoarthritis of any joint; iii) studies that used botulinum toxin type A; iv) studies that applied intra-articular BoNT in a joint. The exclusion criteria were: i) review articles; ii) follow-up periods with less than a month. Two independent reviewers were responsible for the selection and data extraction from each study.

A total of 328 articles were obtained with the initial research - 33 articles from PubMed, 8 articles from Cochrane Central Register of Controlled Trials (CENTRAL) and 287 articles from Scopus. After duplicate removal, 313 remained for screening. The abstract of every article was accessed and 294 articles were excluded for not fulfilling the inclusion or exclusion criteria. The remaining 19 articles were included in this review, according to their scientific relevance.

Every article was adequately reviewed to ensure eligibility and quality criteria were met. The quality criteria evaluated in each article were related to the validity, reliability, replicability and generalizability of the results, regarding the effects of IA BoNT administration in OA treatment of different joints. The schematic of evidence acquisition is presented in Fig. 1.

Data Extraction

Data extraction was based on a pre-defined set of clinical variables and outcomes and was performed by two reviewers. The extracted data from each study were the author names, year of publication, study design, studied joint, studied interventions, outcomes of interest, doses of botulinum toxin and sample characteristics, such as sample size, age and gender. The following outcomes of interest were analyzed: i) pain, quantified with validated scales, such as the Visual Analogic Scale (VAS); ii) clinical scores used to evaluate specific joints, such as the Knee Injury and Osteoarthritis Outcome Score (KOOS); iii) Range of motion (ROM) and QOL scores, such as the SF-36 questionnaire.

Two independent reviewers were responsible for the selection and extraction of the pre-specified data from every

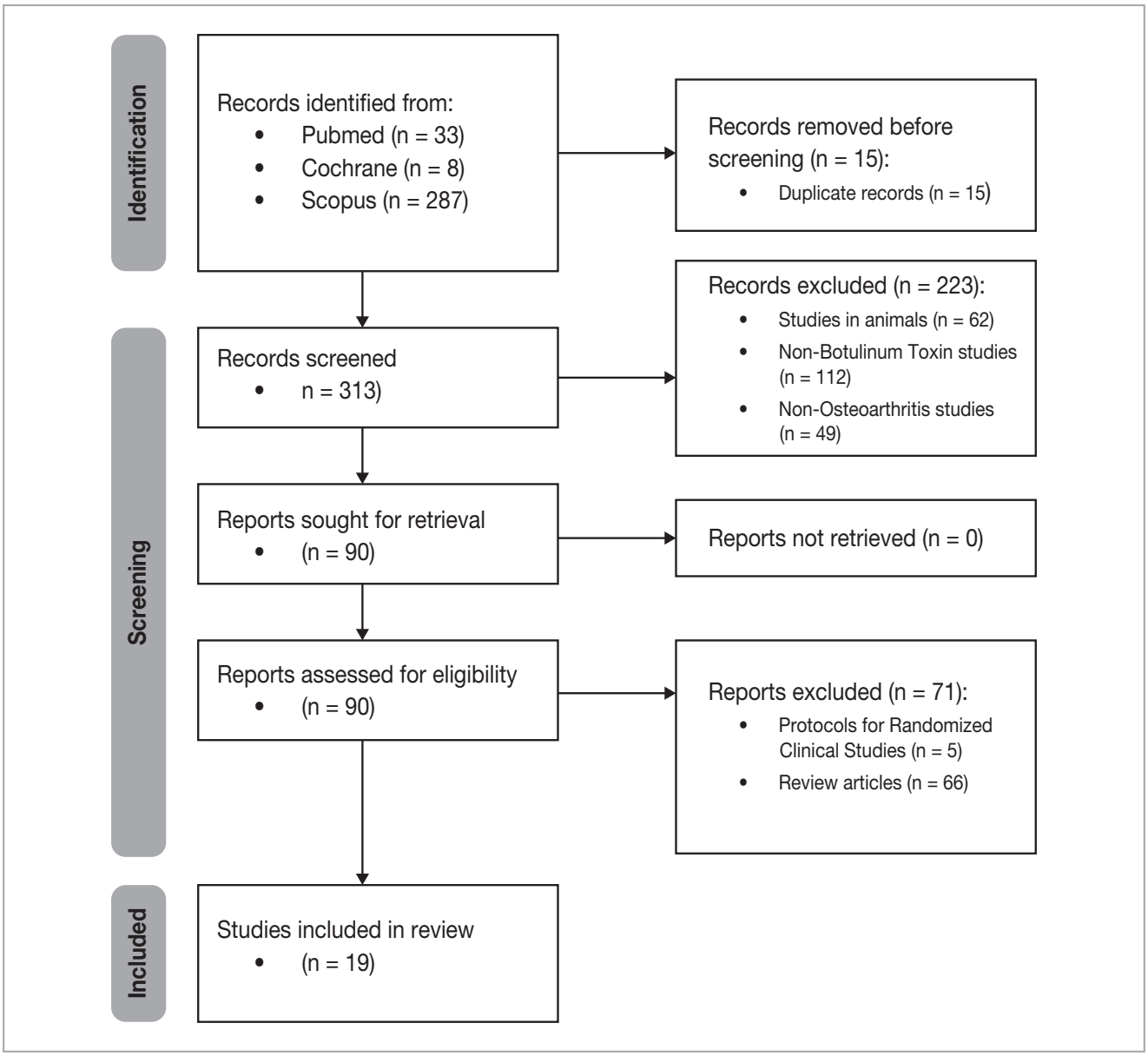

Figure 1 - Identification of studies via databases and registers.

study. Blinding of the reviewers was not performed. In case of disagreement, a third reviewer was responsible for the analysis of the study in question and a team discussion was made to acquire a consensus about the inclusion of the study in the review.

Risk of Bias and Quality Assessment

The risk of bias and quality of each included article was accessed with validated tools by two reviewers, according to the design of each study.

Randomized clinical trials (RCTs) were accessed with the revised Cochrane Risk-of-Bias Tool for Randomized Clinical Trials (RoB2) and non-randomized observational prospective and retrospective studies were evaluated with the Newcastle-Ottawa Scale (NOS).

RoB2 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 each of these domains classify the risk of bias each RCT as low, medium or high.

NOS tool resorts to a star grading system to assess three domains: selection, comparability and outcomes. This tool classifies the quality of each study as having good, fair or poor quality.

The quality of the content of all included studies was assessed and only articles with adequate, useful and non-biased information were used for the elaboration of this systematic review. The risk of bias of the RCTs is represented in Table 1 and the risk of bias of the nonrandomized studies is represented in Table 2.

Table 1 - Risk of Bias of Randomized Clinical Trials, according to Cochrane Risk-of-Bias Tool for Randomized Clinical Trials (RoB2).

	Nielsen *et al*[7]	Mendes *et al*[8]	Boon *et al*[9]	Chou *et al*[10]	Hsieh *et al*[11]	Bao *et al*[12]	McAlindon *et al*[13]	Singh *et al*[14]	Rezasoltani *et al*[15]	Noorbaloochi *et al*[16]	Hashemi *et al*[17]	Sun *et al*[18]	Najafi *et al*[18]
Randomization process	+	+	+	-	-	+	+	+	?	+	+	+	-
Deviation from the intended intervention	+	+	+	+	?	+	+	+	?	+	+	+	?
Missing outcome data	?	?	+	+	+	+	?	?	+	?	+	+	+
Measurement of the outcome	+	?	+	?	?	+	+	+	+	+	+	+	+
Selection of reported result	?	+	+	+	+	+	+	+	+	+	+	+	?

+ low risk of bias; ? some concerns; - high risk bias

Table 2 - Risk of bias of nonrandomized studies, according to Newcastle Ottawa Scale (NOS).

	Mahowald *et al*[20]	Sari *et al*[21]	Batifol *et al*[22]	Ko *et al*[23]	Kushnaryov *et al*[24]	Vázquez *et al*[25]
Selection	**	***	***	*	**	**
Comparability	*	*	*	*	*	*
Outcome	*	***	**	*	**	**

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Results

Study Designs and Baseline Characteristics

This review included a total of 19 articles that fulfilled the predefined criteria: 13 RCTs, one observational prospective study, three observational retrospective studies, one case series and one case report. Table 3 summarizes the design and characteristics of each included study and Table 4 presents the used scores and obtained outcomes.

The total number of patients in the included studies varied from one to 200, the evaluation time range went from one to 21 months and the botulin toxin dose range went from 15 to 400 units.

Table 3 - Study Designs and Baseline Characteristics.

Author	Year of Publication	Study Design	Year	Joint	Interventions / Comparison	n	Mean age	Sex (male)	Dosage of BoNT-A (Units)	Follow-up Assessments
Nielsen *et al*[7]	2016	RCT	2016	Knee	IA BoNT-A vs IA SS 0,9%	61 / 60	62.5 / 62.1	29 / 30	200	1, 2 and 3 months
Mendes *et al*[8]	2018	RCT	2019	Knee	IA BoNT-A vs IA TH vs IA SS 0,9%	35 / 35 / 35	62.5 / 65.5 / 64.6	3 /4 /2	100	1, 2 and 3 months
Boon *et al*[9]	2010	RCT	2010	Knee	IA BoNT-A low dose vs IA BoNT-A high dose vs IA MA	20 / 20 / 20	64.1 / 61.2 / 60.8	9 /9 / 7	100 / 200	3 and 6,5 months
Chou *et al*[10]	2010	Nonrandomized clinical trial	2010	Knee	IA BoNT-A	38 / 38	73.4 / 73.4	13 / 13	100	1, 2, 3, 4, 5, and 6 months
Hsieh *et al*[11]	2015	RCT	2016	Knee	IA BoNT-A vs Physical Exercise	21 / 20	67.8 / 68.1	8 / 8	100	1 week and 6 months
Bao *et al*[12]	2018	RCT	2018	Knee	IA BoNT-A vs IA Hyaluronate vs IA SS 0,9%	20 / 20 / 20	66.4 / 66.0 / 65.3	10 / 13 / 9	100	1 and 2 months
Mahowald *et al*[20]	2006	Retrospective case series	2006	Shoulder, Knee and Ankle	IA BoNT-A	11	62.0	9	20 to 100	12 months
MacAlindon *et al*[13]	2018	RCT	2018	Knee	IA BoNT-A low dose vs IA BoNT-A high dose vs IA SS 0,9%	43 / 44 / 89	60.2 / 60.7 / 61.1	17 / 14 / 38	200 to 400	6 months
Singh *et al*[14]	2015	RCT	2015	Knee	IA BoNT-A vs IA SS 0,9%	23 / 26	67.1 / 66.8	18 / 23	100	2 weeks and 1,2,3,4 and 6 months
Sari *et al*[21]	2019	Retrospective cohort	2022	Temporomandibular Joint	Arthrocentesis vs Arthrocentesis + IA BoNT-A	15 / 15	29.9	3 / 2	15	1 week, 1 month and 6 months

Rezasoltani *et al*[15]	2021	RCT	2021	Knee	IA BoNT-A vs Physical Therapy	100 / 100	77.7 / 63.0	27 / 20	100	1,3 and 6 months
Najafi *et al*[19]	2019	Nonrandomized clinical trial	2019	Knee	IA BoNT-A	46	67.3	6	250	1 month
Hashemi *et al*[17]	2018	RCT	2018	Shoulder	IA BoNT-A vs IA TH	25/25	53.0	24	100	3 months
Batifol *et al*[22]	2018	Retrospective Cohort	2018	Temporomandibular Joint	IA BoNT-A	77	46.0	25	30	15 days, 1 month and 3 months
Ko *et al*[23]	2018	Case Report	2018	Knee	IA BoNT-A	1	88.0	0	150	3 months
Kushnaryov *et al*[24]	2009	Retrospective Case Series	2009	Shoulder, Knee and Ankle	IA BoNT-A	11	62.9	9	30 to 150	21 months
Sun et al[18]	2014	RCT	2014	Ankle	IA BoNT-A vs IA Hyaluronic Acid	38 / 37	50.1	23 / 23	100	6 months
Noorbaloochi *et al*[16]	2009	RCT	2009	Shoulder	IA BoNT-A vs SS 0,9%	21 / 22	72.1 / 70.2	20 / 22	100	1 month
Vázquez *et al*[25]	2011	Prospective Cohort	2011	Knee	IA BoNT-A	12	72.0	0	100	4 months

IA – intra-articular; BoNT-A – botulinum toxin type A; SS 0,9% - saline solution 0,9%; TH – triamcinolone hexacetonide; RCT – randomized clinical trial; MA – methylprednisolone acetate.

Table 4 - Study Scores and Outcomes.

Author	Scores	Results	Overall BoNT-A Performance
Nielsen *et al*[7]	PPT, VAS, WOMAC, ADP, GIC	IA BoNT-A injection with a single dose was observed to have a clinical benefit in pain control, pain sensitization and function when compared to placebo. Subjects with highest values of average pain showed significant effects on the various experimental sensitization parameters studied.	BoNT-A +
Mendes *et al*[8]	VASr, VASm, ROM, 6MWT, TUG, WOMAC, ROM and US-SH	IA TH injections were related to better short-term (after 1 month) outcomes in terms of VASm, WOMAC and US-SH scores. No differences were found between IA BoNT-A, TH and SS 0,9% in long term outcomes (2 and 3 months).	BoNT-A -
Boon *et al*[9]	VAS, WOMAC, 40 m walk test, SF-36	Low or High dose of IA BoNT-A and cortisone injections were related to better pain, functional and quality of life outcomes at 3 month follow-up. However, after 6,5 months of follow-up, the effects of this substances were attenuated.	BoNT-A =
Chou *et al*[10]	WOMAC	IA BoNT-A injection provided better clinical outcomes related to pain, stiffness and physical function in every follow-up assessment when compared to baseline, according to WOMAC score. However, no statistical differences where found.	BoNT-A +

Hsieh *et al*[11]	VAS, Lequesne and WOMAC	Short and long-term outcomes related to pain control and function are improved after IA BoNT-A injection. Subjects submitted to IA BoNT-A also had reduced consumption of acetaminophen, when compared to the control group.	BoNT-A +
Bao *et al*[12]	VAS, WOMAC, SF-36, PCS-36, MCS-36	IA BoNT-A has better outcomes when compared to IA hyaluronate or placebo, specially if followed by therapeutic exercises with manual therapy to improve muscle strength, balance and functional mobility.	BoNT-A +
Mahowald *et al*[20]	VAS	Subjects submitted to IA BoNT-A reported better pain control in long-term. However, different doses and follow-up periods were applied for each subject, which may condition the obtained results.	BoNT-A+
MacAlindon *et al*[13]	VAS, WOMAC, GIC	Both IA BoNT-A and SS 0,9% reduced pain and improved functional activity in a similar way. However, a post-hoc analyses suggested that IA BoNT-A reduces nociceptive pain in knees affected with OA.	BoNT-A =
Singh *et al*[14]	VAS, WOMAC, ROM, TUG, MPQ, SF-36	One administration of IA BoNT-A was related to a significantly reduction of pain and improvement of pain stiffness and overall function in patients with chronic knee pain after total knee arthroplasty.	BoNT-A +
Sari *et al*[21]	VAS, ROM	Arthrocentesis followed by IA BoNT-A provides pain control and contributes to mouth opening improvement in subjects in chronic temporomandibular dysfunction.	BoNT-A +
Rezasoltani *et al*[15]	VAS, KOOS	IA BoNT-A injection can improve pain and overall function in subjects with chronic pain in knee OA, having long-term benefits.	BoNT-A +
Najafi *et al*[19]	VAS, ROM, KOOS	IA BoNT-A reduces subjective pain in subjects with knee AO and decreases overall severity of symptoms such as joint stiffness, clicking and locking.	BoNT-A +
Hashemi *et al*[17]	VAS, ROM	Subjects with glenohumeral osteoarthritis submitted to IA BoNT-A present lower levels of pain intensity and better overall shoulder ROM.	BoNT-A +
Batifol *et al* [22]	VAS, ROM, SF-36	BoNT-A injected in the temporomandibular joint provides pain reduction and improves mouth-opening and quality of life of subjects in chronic temporomandibular disorder.	BoNT-A +
Ko *et al*[23]	WOMAC	Administration of IA BoNT-A reduces pain, stiffness and difficulty in performing daily activities, according to WOMAC score.	BoNT-A +
Kushnaryov et al[24]	NRS	Repeated injections of IA BoNT-A between intervals of 3 to 17 months contributes to chronic and refractory OA pain management of shoulder, knee and ankle joints.	BoNT-A +
Sun *et al*[18]	AOFAS, VAS, SLS, TUG	No difference was found between IA BoNT-A and Hyaluronic Acid in terms of pain and functional activity in patients with ankle osteoarthritis. However, both treatments seem to have clinical long-term benefits.	BoNT-A =
Noorbaloochi *et al*[16]	VAS, ROM, SPADI, MPQ	Subjects with chronic refractory shoulder pain have significant better short-term outcomes in terms of pain control and ROM after injection of IA BoNT-A, when compared to placebo.	BoNT-A +

Vázquez *et al*[25]	VAS, WOMAC	IA BoNT-A was related to pain relief and optimal WOMAC score, when compared to baseline.	BoNT-A +

IA – intra-articular; BoNT-A – botulinum toxin type A; BoNT-A + – favorable effect of BoNT-A; BoNT-A - – non favorable effect of BoNT-A; BoNT-A = – no difference between BoNT-A and control group; PPT – pressure pain threshold; ADP – average daily pain; GIC – global impression of change; TH- triamcinolone hexacetonide; VASr – Visual Analogic Scale in Rest; VASm- Visual Analogic Scale in Motion; ROM – range of motion; 6MWT -6 Minute Walk Test; TUG – Timed Up and GO; WOMAC – Western Ontario and McMaster Universities Arthritis Index ; US-SH – ultrasound of synovial hypertrophy; SPADI – Shoulder Pain and Disability Index; MPQ - McGuill Pain Questionnaire; NRS – Numeric Rating Scale; KOOS – Knee injury and Osteoarthritis Outcome Score; OA – osteoarthritis; AOFAS – American Orthopedic Foot and Ankle Score; SLS -Single Leg Stance test

Botulinum Toxin

Eight included studies assessed subjects before and after the administration of IA BoNT-A - four studies explored the effects of BoNT-A in the knee, two studies in the shoulder, knee and ankle and two studies in the temporomandibular joint. The number of patients that participated in these studies varied from one to 77 and the dosage of BoNT-A used went 20 to 150 units. The follow-up period of these studies varied from 1 to 21 months and the evaluation times were different according to each study protocol. Every study included in this category revealed improvement of pain, ROM and functional outcomes after the administration of IA BoNT-A.

Sari *et al* studied subjects with chronic temporomandibular disfunction which were submitted to arthrocentesis.[21] A total of 15 subjects submitted to this intervention were also submitted to IA BoNT-A administration and a comparison was made with subjects submitted to arthrocentesis that was not followed by BoNT-A administration. After a 6 month follow-up period, patients submitted to BoNT-A reported better VAS scores and ROM.[21]

Botulinum Toxin versus Saline Solution

Five studies compared the effect of IA BoNT-A with IA 0.9% saline solution in the knee joint. The number of participants varied from 43 to 176 and used BoNT-A units went from 100 to 400 units. The follow-up period of these studies varied between 1 and 6 months and the evaluation times were different, according to each study protocol. However, most studies made at least one evaluation 1 month after the intervention.

Four studies reported better clinical short and long-term outcomes related to IA BoNT-A in terms of pain control and function optimization.[7,12,14,16] However, Mendes *et al* revealed that despite promoting short-term pain control and early ROM improvement, when compared to IA saline solution, IA BoNT-A did not have better long-term outcomes.[8] Also, despite suggesting IA BoNT-A can reduce nociceptive activity related to knee OA, MacAlindon *et al* reported IA BoNT-A and IA saline solution reduces knee OA pain and improves WOMAC and GIC scores similarly.[13]

Botulinum Toxin versus Corticosteroids

Two studies compared IA BoNT-A with IA triamcinolone hexacetonide and one study compared IA BoNT-A to IA methylprednisolone acetate.

Mendes *et al* included 105 participants in its study and used 100 units of BoNT-A. The evaluation times were at 1, 2 and 3 months after the date of the intervention. This study reported better pain control during motion, WOMAC score and reduced ultrasound-detected synovial hypertrophy when subjects in knee OA were submitted to IA TH, when compared to IA BoNT-A.[8]

Hashemi *et al* included 50 participants and used a dosage of 100 units of BoNT-A. The evaluation time of this study was 3 months after the intervention. This study reported better pain control and overall range of motion of patients with glenohumeral osteoarthritis submitted to IA BoNT-A, when compared to IA TH.[17]

Boon *et al* assessed the effect of low and high doses of IA BoNT-A and IA Methylprednisolone Acetate in subjects with knee OA. This study included 60 participants, studied the effect of 100 and 200 units of IA BoNT-A and evaluated the participants 3 and 6.5 months after the intervention date. It concluded that pain and functional outcomes were equally improved in the short term, however, the clinical benefits of both these interventions seemed to be attenuated in a long-term perspective.[9]

Botulinum Toxin versus Hyaluronic Acid

Sun *et al* compared the administration of 100 units of IA BoNT-A and IA hyaluronic acid outcomes in 75 subjects with ankle OA.[18] Despite reported pain and functional benefits after a 6-month follow-up period, there were no statistically significant differences between both groups, which means IA BoNT-A and IA hyaluronic acid seemed to have similar effects in ankle OA.[18]

Botulinum Toxin versus Physical Therapy or Physical Exercise

Hsieh *et al* compared the effect of 100 units of IA BoNT-A with physical exercise in 41 subjects with knee OA. Participants were evaluated 1 week and 6 months after the intervention. It was concluded that short and long-term pain and functional outcomes are improved in the IA BoNT-A group, despite the benefits presented in the group submitted to physical exercise.[11] In this study, subjects in the IA BoNT-A group also had less consumption of acetaminophen for pain management.[11]

Rezasoltani *et al* studied the effects of 100 units of IA BoNT-A in 200 subjects with knee OA and compared it to an

exclusive physical therapy program. Participants were evaluated after 1, 3 and 6 months of IA BoNT-A administration. In this study, subjects in the IA BoNT-A group presented better VAS and Knee Injury and Osteoarthritis Outcome Score (KOOS) results.[15]

Discussion

Recent studies suggest that OA has an inflammatory component, rather than being simply a non-inflammatory degenerative joint disease.[26] Inflammatory cytokines, such as interleukin (IL)-β and tumor necrosis factor (TNF)-α produced by the synovial membrane and chondrocytes can be detected in the synovial fluid of patients with OA. [26]

Injury and inflammation can lower Aδ, Aβ, and C nerve fibers excitation threshold, which are present in joint histological structures. Aδ fibers seem to be sensitized by TNF-α, while C fibers may be sensitized by TNF-α, IL-6 or IL-1β that can arise from noxious stimuli.[27] Chronic joint inflammation is also associated with hyperexcitability of spinal nociceptive neurons, which is known by central sensitization.[28] However, neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) also play an important role in pain generation outside the spine through sensitization of nerves and nociceptors, which is a process known as peripheral sensitization.[29]

BoNT-A may inhibit central and peripheral 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 BoNT-A administration.[30] 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, reducing pain propagation resulting from peripheral stimuli.[30] These reductions in peripheral sensitization and afferent input to the spinal cord from peripheral nerve endings may indirectly decrease the central sensitization process. BoNT-A may also be retrogradely transported along the axons and modulate neuronal activity in the central nervous system, through stimulation of inhibitory gamma-aminobutyric acid (GABA)-A receptors and μ opioid receptors in the spinal cord. All these biochemical processes may explain why BoNT-A seems to have clinical benefits related to OA pain management, which can eventually lead to improvement of patients integration in rehabilitation programs and promote overall long-term functional benefits.

The included studies in this systematic review presented fair to good quality and the overall impression seems to favor IA BoNT-A administration in OA of different joints in comparison to placebo and other conventional treatments such as IA corticosteroids or physical therapy. Pain and functional scores were generally improved with IA BoNT-A. Only one study reported better short-term outcomes with IA corticosteroid administration when compared to IA BoNT-A.[8] Three studies, however, showed no differences between BoNT-A and other interventions – Boon *et al* reported no differences in clinical outcomes between IA BoNT-A and methylprednisolone acetate[9]; MacAlindon *et al* reported no differences between IA BoNT-A and IA saline solution[13]; Sun *et al* reported no differences between IA BoNT-A and IA hyaluronic acid.[18]

This review has several limitations related to the currently available evidence of IA BoNT-A in OA management. There was a relatively small number of studies included in the review and the sample sizes of each study were considerably reduced. There was also important heterogeneity between the included studies not only related to the applied scores, but also to the measurement of the outcomes of interest. BoNT-A dosages varied from study to study and this variation may explain the differences obtained in each study. Also, several clinical trials included presented a lack of blinding randomization, which may have biased the obtained results.

A meta-analysis of the obtained results was not performed due to the heterogeneity of the used scores and measured outcomes.

BoNT-A price is also a limitation that may compromise OA treatment with IA administration. However, the included studies did not analyze the cost of IA BoNT-A treatment, which compromised the elaboration of a treatment cost analysis.

Conclusion

IA BoNT-A injection seems to have clinical long-term benefits related to pain control and function improvement of temporomandibular, shoulder, knee and ankle joints. However, the included studies are heterogenous and have reduced sample sizes and methodological differences between them. More RCTs with higher sample sizes should be performed to determine the effective dosages and optimal dilution to administer IA BoNT-A for each joint.

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