

SYSTEMATIC REVIEW

Botulinum Toxin A for Post-Arthroplasty Complications:
A Systematic Review of Efficacy and Safety in TKA and THA

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Abstract

Objectives: To systematically review and synthesize available human studies investigating the efficacy and safety of botulinum neurotoxin type A (BoNT/A) injections for managing complications following total knee arthroplasty (TKA) and total hip arthroplasty (THA).

Methods: A systematic search of Medline/PubMed, Web of Science, Scopus, and Embase was conducted up to May 2025 per PRISMA 2020 guidelines. Eligible studies enrolled adults who had undergone THA or TKA and received ≥ 50 units (U) of intra-articular or intramuscular BoNT/A for postoperative pain, stiffness, or musculoskeletal dysfunction. The assessed outcomes included range of motion (ROM), pain scores measured using the Visual Analog Scale (VAS) or Numeric Rating Scale (NRS), functional scores including the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Harris Hip Score (HHS), Knee Society Score (KSS), and adverse events.

Results: Thirteen studies met the inclusion criteria, including two RCTs and eleven case studies, with a total of 92 patients. In patients undergoing TKA, BoNT/A was primarily injected into hamstring or gastrocnemius muscles, with doses from 50 to 400 U. Improvements in ROM, KSS, and pain scores were reported in most studies, though statistical significance was inconsistent. In patients undergoing THA, BoNT/A injected into hip adductors, iliopsoas, and tensor fascia lata was associated with reduced flexion contractures and pain, and improved HHS and ODI. No major adverse events were reported; minor effects included bruising and flu-like symptoms.

Conclusion: BoNT/A injections appear to be safe and may be effective for managing chronic pain and flexion contractures following TKA and THA. However, heterogeneity in study design, small sample sizes, limited controls, and variable outcome measures limit the strength of the current evidence. Further high-quality randomized controlled trials are required to establish optimal dosing, timing, injection sites, and to confirm the clinical benefits of BoNT/A in this population.

Level of evidence: III

Keywords: Botulinum toxin type A, Chronic pain, Flexion contracture, Range of motion, Systematic review, Total hip arthroplasty, Total knee arthroplasty

Introduction

Total joint arthroplasties, including total knee arthroplasty (TKA) and total hip arthroplasty (THA), are highly effective surgical procedures that are widely performed to relieve pain and restore function in patients with advanced osteoarthritis. Although these interventions achieve excellent outcomes in most patients, a clinically relevant subset continues to experience postoperative complications that may impair recovery.

These complications include persistent pain, joint stiffness, reduced range of motion (ROM), muscle contractures, and spasticity.¹⁻³ They may result from various factors, including pre-existing neuromuscular conditions, postoperative inflammation, scar tissue formation, and abnormal muscle tone.⁴

Conventional treatments, including physical therapy, analgesics, non-steroidal anti-inflammatory drugs

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(NSAIDs), and, occasionally, more invasive interventions such as manipulation under anesthesia (MUA), are commonly employed to manage these complications. However, in some patients, these therapies fail to produce satisfactory improvements, particularly in those with chronic symptoms or underlying spasticity.⁵

Botulinum neurotoxin type A (BoNT/A), a neurotoxin produced by *Clostridium botulinum*, has gained increasing attention as a promising adjunctive therapy in such cases.⁶ BoNT/A exerts its effects by inhibiting acetylcholine release at the neuromuscular junction, resulting in temporary chemodenervation and muscle relaxation.⁷ This mechanism supports its use in reducing hypertonicity and spastic muscle activity. Beyond its neuromuscular effects, BoNT/A has demonstrated antinociceptive properties through modulation of peripheral and central pain pathways, including inhibition of substance P, calcitonin gene-related peptide (CGRP), and glutamate release—neurotransmitters involved in chronic pain sensitization.^{6,7}

These dual mechanisms—muscle relaxation and pain modulation—have led to the widespread use of BoNT/A in various clinical settings, including dystonia, cerebral palsy, chronic migraine, spasticity secondary to stroke or multiple sclerosis, and musculoskeletal pain syndromes.⁶ More recently, its use has been extended to orthopedic conditions, such as refractory shoulder pain and knee osteoarthritis. A 2024 meta-analysis by Yang et al.⁸ confirmed the safety and efficacy of BoNT/A injections using various injection techniques, including intra-articular glenohumeral injection via an anterior or posterior approach, subacromial bursa injection, and trigger-point palpation techniques, for the management of chronic shoulder pain, demonstrating significant improvements in both pain and shoulder function. In addition, intra-articular BoNT/A injections in patients with knee osteoarthritis (KOA) have demonstrated comparable or superior outcomes to corticosteroids and hyaluronic acid in terms of pain reduction and functional improvement across WOMAC domains.⁹

In the context of joint arthroplasty, BoNT/A has been investigated as a therapeutic option for managing post-TKA and post-THA complications, particularly in patients with flexion contractures, persistent joint pain, or muscle imbalances.^{10,11} Several studies have reported improvements in range of motion (ROM), functional scores such as the Knee Society Score (KSS) and Harris Hip Score (HHS), and reductions in pain scores measured by the Visual Analog Scale (VAS) and Numeric Rating Scale (NRS); however, findings across the literature have been inconsistent and often limited by small sample sizes and heterogeneous study methodologies.¹⁰⁻¹² Notably, BoNT/A has generally demonstrated a favorable safety profile, with only mild adverse effects reported, including localized pain, bruising, transient muscle weakness, and flu-like symptoms.^{4,10,13,14}

Given these promising yet inconclusive findings, a comprehensive synthesis of the available evidence is warranted. Therefore, this study aimed to systematically review all primary human studies evaluating the use of BoNT/A in lower-limb joint arthroplasty, with a focus on its effects on pain, joint function, range of motion (ROM), and adverse events. This review provides an evidence-

based perspective on the clinical value of BoNT/A for managing postoperative complications following TKA and THA.

Materials and Methods

PRISMA 2020 guidelines were followed by all co-authors to conduct the current study.¹⁵ The study protocol was registered at PROSPERO under code number CRD42024555894.

Literature Search

Medline via PubMed, Web of Science, Scopus, and Embase were systematically searched up to May 2025. The search strategy was developed in accordance with the recommendations of the Cochrane Collaboration. Keywords and Medical Subject Headings (MeSH) related to “botulinum toxin A,” “knee arthroplasty,” and “hip arthroplasty” were combined using Boolean operators, including “OR” and “AND” (Supplementary File 1). In addition to screening the database search results, the reference lists of the included full-text articles were manually reviewed to identify potentially eligible publications not retrieved through the electronic search.

Eligibility criteria

Studies were included or excluded based on predefined eligibility criteria. The inclusion criteria, structured according to the PICO framework, were as follows:

Patients: Adults who had undergone total hip arthroplasty (THA) or total knee arthroplasty (TKA) and were experiencing stiffness, chronic pain, or other musculoskeletal complications related to the operated joint.

Intervention: Intra-articular or intramuscular injection of BoNT/A at a dose of ≥ 50 units.

Control: Studies including a control group of patients who did not receive BoNT/A were eligible; studies without a control group were also considered.

Outcomes: Primary outcomes included functional assessments using the Harris Hip Score (HHS), Knee Society Score (KSS), range of motion (ROM), and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Secondary outcomes included the Oswestry Disability Index (ODI) for activity limitation, the Medical Research Council (MRC) scale for muscle strength, the Modified Ashworth Scale (MAS) for muscle tone, and pain assessment using the Visual Analog Scale (VAS) or Numeric Rating Scale (NRS).

Exclusion Criteria

Studies were excluded if they met any of the following criteria: non-English language publications; studies for which the full text was not available; non-quantitative publications, including review articles, letters to the editor, book chapters, or editorials; and studies lacking essential information on patient demographics, indications for BoNT/A injection, or reported outcomes.

Study selection

Two independent reviewers (A.H.S. and M.S.) screened the titles and abstracts of all records exported to EndNote 9 to identify potentially eligible articles for full-text review. The full-text articles were then independently assessed by the

same reviewers to determine final inclusion. Any disagreements or discrepancies in study selection were resolved through discussion with a third independent reviewer (A.M.A.).

Data extraction

Two reviewers (A.H.S. and M.S.) independently extracted the following data from each included study: first author's last name, year of publication, country of study, study design, number of patients, patient age, gender distribution, indication for BoNT/A injection, dosage, brand of BoNT/A used, mean time between arthroplasty and injection, and anatomical site of injection.

All outcome measures specified in the eligibility criteria were systematically recorded in a pre-designed Excel spreadsheet for data synthesis.

Quality assessment

The quality of randomized controlled trials (RCTs) was assessed using the Risk of Bias 2 (RoB-2) tool,¹⁶ while case reports and case series were evaluated according to the methodological quality framework proposed by Murad et al.¹⁷

The RoB-2 tool evaluates bias across five key domains: (1) the randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome, and (5) selection of the reported results. Based on the assessment of these domains, studies were categorized as having a "Low risk of bias," "Some concerns," or "High risk of bias," according to the tool's overall judgment algorithm.¹⁶

For case reports and case series, each study was assessed according to four criteria: Selection, Ascertainment, Causality, and Reporting. A response of "Yes" was assigned if a criterion was met, and "No" if it was not. Based on the total number of "Yes" responses, studies were classified as having a "Low risk" (8 points), "Medium risk" (6–7 points), or "High risk" (0–5 points) of bias.

Data Synthesis

Owing to heterogeneity in study designs, outcome measures, and data presentation formats, a meta-analysis was not feasible. Therefore, a descriptive synthesis was conducted to summarize the findings of the included studies narratively and to facilitate interpretation of the available evidence.

Results

Overall result

The systematic database search initially identified 131 publications. After duplicate removal, 92 records underwent title and abstract screening. Of these, 18 articles were selected for full-text review. Ultimately, 13 studies met the predefined inclusion criteria and were included in this systematic review [Figure 1].

Quality assessment

Two randomized controlled trials (RCTs) were evaluated using the Cochrane RoB 2 tool. One study fulfilled all five domains and was rated as having a low risk of bias,¹⁸ whereas the other raised concerns in two domains and was rated as

having some concerns.¹⁰ The remaining 11 studies, consisting of case reports and case series, were assessed using the methodological quality framework proposed by Murad et al.¹⁷ Overall, the methodological quality of the included studies was rated as moderate to high [Figure 2 and Table 1].

TKA

Seven studies investigated the use of BoNT/A in patients following TKA, comprising a total of 77 patients and 82 treated knees. Among the 60 patients for whom sex was reported, 28 (46.6%) were male and 32 (53.3%) were female.

Two of the seven studies were RCTs. Singh et al.¹⁸ included 49 patients with chronic post-TKA pain (mean age, 67.1 ± 10.1 years). Smith et al.¹⁰ investigated BoNT/A for flexion contracture in 14 patients (mean age, 60.4 ± 6.4 years). In these RCTs, BoNT/A was administered to 23 and 9 patients, respectively.

The remaining five studies were case reports or case series involving 45 patients, with ages ranging from 43 to 80 years and sample sizes ranging from 1 to 19 patients. Indications for BoNT/A injection included flexion contracture^{12,19,21} and chronic refractory pain.²² All injections were administered postoperatively [Table 2].

Injection Protocols

RCTs: The two RCTs used different injection approaches: intra-articular injection¹⁸ and intramuscular injection.¹⁰ Smith et al. injected the medial and lateral hamstring muscles with a single 100-unit (U) dose,¹⁰ whereas Singh et al. used a single 100 U intra-articular injection.¹⁸ In both trials, the control groups received saline injections at identical anatomical sites.

Case studies: In the case studies, injections targeted the gastrocnemius^{12,20,21} and hamstring muscles,^{12,19,20} with one study using an intra-articular approach.²² The number of injections ranged from one to three per patient, with doses varying from 50 to 300 U per injection site [Table 2].

Treatment Timeline and Adjunct Therapies

RCTs: In the RCTs, the mean time from surgery to injection was 52.9 days (range, 18–91 days) in the study by Smith et al.,¹⁰ whereas Singh et al. reported a minimum postoperative interval of 6 months.¹⁸ The protocol used by Smith et al. included post-injection physical therapy, use of an extension orthosis, and manipulation under anesthesia (MUA). In contrast, the study by Singh et al. did not include adjunctive therapies during follow-up. Follow-up consisted of three visits over 6 months in Smith et al.¹⁰ and five monthly visits in Singh et al.¹⁸

Case studies: Among the case studies, the mean interval between arthroplasty and injection ranged from 1.5 months¹⁹ to 18 months,^{12,20} with the longest reported interval being 81 months.¹² Patients had received various prior interventions, including MUA,^{19,20} oral anti-inflammatory medications,^{21,22} physical therapy,²¹ posterior capsular release, hamstring tenotomy, and prophylactic peroneal

nerve decompression.²⁰ Follow-up ranged from two visits¹⁹ to seven visits,²² although two studies did not specify the

number of follow-up visits [Table 2].^{12,20}

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

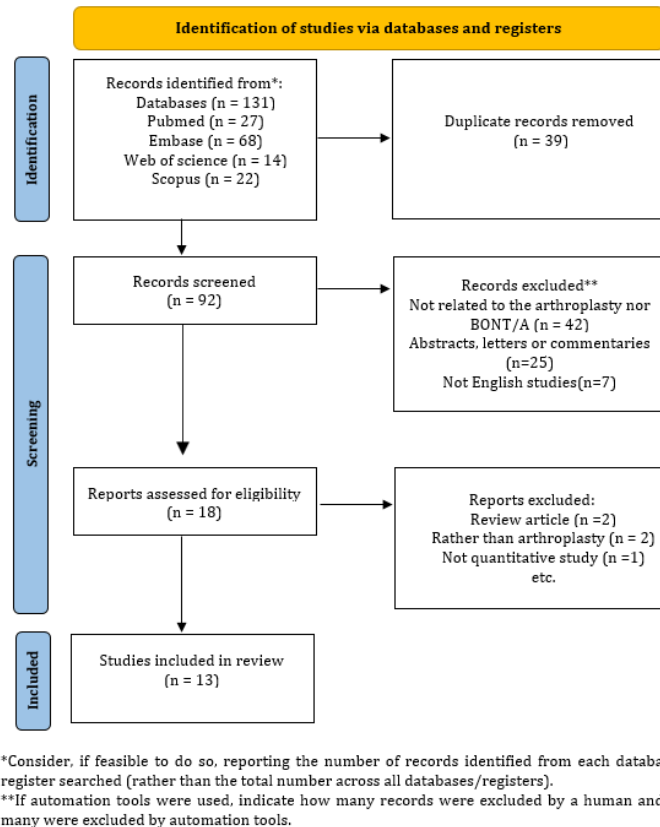


Figure 1. PRISMA flowchart

Figure 2. Risk of bias assessment for included randomized controlled trials using the Cochrane Risk of Bias 2.0 tool

Study	D1	D2	D3	D4	D5	Overall
Singh et al, 2010 ¹⁸	●	●	●	●	●	●
Smith et al., 2016 ¹⁰	●	●	●	●	●	●

Each row represents a study, and each column corresponds to a bias domain:

D1 – Bias arising from the randomization process

D2 – Bias due to deviations from intended interventions

D3 – Bias due to missing outcome data

D4 – Bias in measurement of the outcome

D5 – Bias in the selection of the reported result

Judgements are categorized as low risk (green) or some concerns (yellow). The final column indicates the overall risk of bias per study

Table 1. The Risk of bias of case studies using the methodological quality framework proposed by Murad et al.¹⁷

Study	Selection (Q1)	Ascertainment		Causality				Reporting (Q8)	Overall
		Q2	Q3	Q4	Q5	Q6	Q7		
Cheesman et al, 2024 ¹⁹	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Medium risk
Frost et al, 2021 ⁴	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Medium risk
Vahedi et al, 2020 ²⁰	Yes	Yes	Yes	No	Yes	n/a	Yes	Yes	Medium risk
Singh et al, 2014 ²²	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low risk
Eibach, 2011	No	Yes	Yes	No	No	No	Yes	Yes	High risk
Bhave et al, 2009 ¹⁴	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Medium risk
Santamaro et al, 2009 ²³	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Medium risk
Bertoni et al, 2008 ¹¹	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Medium risk
Fish et al, 2007 ²⁴	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Medium risk
Seyler et al, 2007 ⁶	Yes	Yes	Yes	No	Yes	n/a	Yes	Yes	Medium risk
Shah et al, 2005 ²¹	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Medium risk

Each row represents a study, and each column corresponds to a bias domain and questions:

Domain 1: Selection (Q1): Does the patient(s) represent the whole experience of the investigator (center), or is the selection method unclear to the extent that other patients with a similar presentation may not have been reported?

Domain 2: Ascertainment (Q2): Was the exposure adequately ascertained? (Q3): Was the outcome adequately ascertained?

Domain 3: Causality (Q4): Were other alternative causes that may explain the observation ruled out? (Q5): Was there a challenge/rechallenge phenomenon? (Q6): Was there a dose-response effect? (Q7): Was follow-up long enough for outcomes to occur?

Domain 4: Reporting (Q8): Is the case(s) described with sufficient detail to allow other investigators to replicate the research or to allow practitioners to make inferences related to their own practice?

Table 2. Study Characteristics and Outcomes of TKA studies.

Study	Country	Study Design	Patients (number)	Mean Age $\pm$ SD (years)	Male Gender (number)	BONT/A ⁸ Dosage/ Site	Timing of injection (post-op or pre-op)	Follow-ups (months)	Primary Clinical Outcome	Adverse Events	Other Treatments in Addition to BONT/A Injection
Smith et al., 2016 ¹⁰	USA	RCT*	BONT/A group: 9 Control group: 5	BONT/A group: 60.4 $\pm$ 6.4 years Control group: 62.5 $\pm$ 14.7 years	BONT/A group: 3 Control group: 3	100 U/ hamstring	1.7 months post-op	1, 6, 12 months	ROM* improved (113°); No diff vs control (p= ns ^a).	Bruising	PT* and knee extension orthosis, In BONT/A group 3 patients underwent MUAx
Singh et al, 2010 ¹⁸	USA	RCT	BONT/A group: 23, Control group: 26	BONT/A group: 67.1 $\pm$ 10.1 years Control group: 66.8 $\pm$ 11.5 years	BONT/A group: 18 Control group: 23	100 U/ Intraarticular	> 6 months post-op	1, 2, 3, 4, and 6 months	VAS ^a pain decreased (p=0.09). WOMAC ^b scores significantly improved (p=0.02).	Mild (Similar to placebo)	.
Cheesman et al, 2024 ¹⁹	USA	Case series	8	66 $\pm$ 5 years	3	Variable/ Hamstring	3.5 months post-op	0.75 and 3.25 months	ROM improved by 9°; all <5° extension deficit.	None	Two to four weeks of aggressive PT plus home exercises

Table 2. Continued

Vahedi et al, 2020 ²⁰	USA	Case series	19	60 ± 5 years	3	300–400 U/ Gastrocnemius, Hamstring	18 months post-op	18 months	KSS ^γ improved by 35 pts (p=0.008).	None	U-splint or bivalved cast for 1 month plus PT 5 days per week for a total of 2–4 months, extension-assist bracing and nighttime cast wear
Singh et al, 2014 ²²	USA	Case series	9	68 ± 12 years	-	100–300 U/ intraarticular	-	1–28 months	57% had ≥50% pain reduction at 4 months.	No major	-
Seyler et al, 2007 ⁶	USA	Case series	8	-	-	100 U/ Gastrocnemius, Hamstring	18 months post-op	-	KSS improved 35 pts; ROM improved 42°.	No major	A rehabilitation regimen that consisted of inpatient and outpatient treatment for eight continuous weeks
Shah et al, 2005 ²¹	USA	Case-report	1	61 years	1	200 U/ Hamstring	1.5 months post-op	0.25 to 6 months	ROM improved from 75° to 117°.	None	MUA, A static progressive extension orthosis and rigorous PT

δ BONT/A: Botulinum toxin type A, *ROM: Range of Motion, γ KSS: Knee Society Score, ηVAS: Visual Analog Scale, χMUA: Manipulation Under Anesthesia, +PT: Physical Therapy, ×RCT: Randomized Controlled Trial, ans: not significant, μ WOMAC: Western Ontario and McMaster Universities Osteoarthritis Indices, φBMI: Body Mass Index

Clinical Outcomes and Safety

RCTs: In the RCT by Smith et al., a significant improvement in knee extension was reported at 12 months ($p = 0.04$); however, no statistically significant improvement in overall range of motion (ROM) was observed compared with the control group.¹⁰ Singh et al. reported a statistically significant reduction in Visual Analog Scale (VAS) pain scores within the BoNT/A group at 2 months ($p = 0.02$); however, the between-group difference in mean VAS scores was not statistically significant ($p = 0.09$).¹⁸ None of the secondary outcomes, including the Timed Stands Test, Timed Up and Go Test, active flexion and extension, McGill Pain Questionnaire–Short Form (SF-MPQ), and most SF-36 subscales, showed significant improvement. Notable reductions were observed in the total WOMAC score and its subscales, except for the pain domain.¹⁸

Regarding safety, Smith et al. reported mild bruising at the injection site in both groups.¹⁰ Singh et al. observed minor adverse events, including bruising, back pain, and headache, with similar frequencies between groups. The incidence of major complications was higher in the control group; however, this difference was not statistically significant ($p = 0.47$).¹⁸

Case studies: Among the case studies, significant improvements in KSS were reported, with one study noting a 35-point increase.^{12,20} ROM improved in all studies that assessed this outcome,^{12,19,20} although only one study reported a p-value.¹² One study assessing knee flexion found no statistically significant improvement.²⁰ No major adverse events were reported in the case studies [Table 2].

THA

Six case studies, involving a total of 15 participants and 19 treated hips, evaluated the effects of intramuscular BoNT/A injections in patients who had undergone THA.^{4,11,13,14,23,24} Four studies investigated postoperative injections for indications of muscle contracture^{14,23} or chronic pain.^{11,24} The remaining two studies, by Frost et al.⁴ and Eibach et al.,¹³ focused on preoperative BoNT/A administration in patients with spasticity.

Injection Protocols

The reported injection sites included the hip adductors,^{4,11,13,23} iliopsoas,^{11,13} tensor fasciae latae,^{4,14} rectus femoris,¹⁴ and gluteus maximus.¹¹ All studies administered a single BoNT/A injection per session, except for Fish et al.,²⁴ which reported two treatment sessions. Doses ranged from 50 to 200 U, with variability observed even for the same muscle. For instance, the iliopsoas was injected with 100 U in one study²⁴ and 200 U in another,¹³ whereas the adductor magnus received 150 U²³ and 100 U,¹⁴ respectively.

Treatment Timeline and Adjunct Therapies

The interval from THA to injection ranged from 2 weeks to 12 months, although one study did not report this information [Table 3].²³ Before BoNT/A administration, some patients received medications, including analgesics,¹¹ benzodiazepines,²³ gabapentin,²³ or a local anesthetic (Xylocaine).²³ Physical therapy was also used in some cases.^{23,24} The number of follow-up visits ranged from one to seven, with post-injection observation periods ranging from 3 days to 62 months, the latter reported by Bhavé et al. [Table 3].¹⁴

Clinical outcomes and safety

ROM was assessed in all studies except one,⁴ with most reporting notable improvements following BoNT/A injection [Table 3]. Pain scores measured using the VAS were reduced in several studies.^{13,23} The HHS also showed significant improvement in two reports.^{14,23} In the case reported by Fish et al.,²⁴ the ODI improved to 18% after 6 months.

Regarding neuromuscular assessments, findings were mixed. Bertonni et al.¹¹ reported no significant changes in

muscle strength, as measured by the MRC scale; muscle tone, as assessed by the Modified Ashworth Scale (MAS); or spasticity. In contrast, Santamato et al.²³ observed a 2-point increase in MRC score, whereas Eibach et al.¹³ reported a 2-point reduction in MAS score [Table 3].

No major adverse events were reported in any of the studies, except for Bhavé et al.,¹⁴ who described mild flu-like symptoms and localized swelling following injection.

Table 3. Study Characteristics and Outcomes of THA studies.

Study	Country	Study Design	Patients (number)	Mean Age $\pm$ SD (years)	Male Gender (number)	BoNT/A ^b Dosage/ Sites	Timing of injection (post-op or pre-op)	Follow-ups (months)	Primary Clinical Outcomes	Adverse Events	Other Treatments Before BoNT/A Injection
Frost et al, 2021 ⁴	Canada	Case report	1	64 years	0	200 U/ hip adductors and tensor fasciae latae	0.5 month pre-op	0.5 month	Reduced pain; improved gait.	None	Conservative management for SCI
Eibach et al, 2011 ¹³	Germany	Case report	1	47 years	1	300 U/ Iliopsoas and adductor magnus	0.5 month pre-op	0.25 to 2 months	Muscle tone (MAS ^a): 3 $\rightarrow$ 1, Pain (VAS): 75% $\rightarrow$ 0%	None	Oral baclofen
Santamato et al, 2009 ²³	Italy	Case report	1	34 years	0	150 U/ Adductor magnus	-	0.25, 0.75, and 2 months	VAS ^a : 7 $\rightarrow$ 2; HHS ^a : 16 $\rightarrow$ 59; Quadriceps strength (MRC ^a): 3 $\rightarrow$ 5; ROM ^a : Improved.	None	NSAIDs, benzodiazepines, gabapentin, physical therapy (laser, ultrasound), xylocaine block, massage
Bhavé et al, 2009 ¹⁴	USA	Case series	10	48 $\pm$ 7.8 years	2	100 U/ Adductor muscles, tensor fascia lata, and rectus femoris	11 months post-op	20 months	ROM improved 23°; HHS: 74 $\rightarrow$ 96.	Flu-like symptoms.	Standard physical therapy (3 $\times$ /week for $\geq$ 2 months) including range of motion exercises, strengthening, and deep heat treatments
Bertonni et al, 2008 ¹¹	Italy	Case report	1	69 years	0	200 U/ Gluteus Maximus	1 month post-op	0.1 to 16 months	VAS: 7 $\rightarrow$ 0; Full pain resolution.	None	NSAIDs (ketoprofen), myorelaxants (tiocholticos), physical therapy, cryotherapy, shoe lift correction, intra articular steroid injections

Table 3. Continued

Fish et al, 2007 ²⁴	USA	Case report	1	71 years	0	100 U/ Iliopsoas	13 months post-op	1 and 6 months	ODI†: 26% → 18%; transient pain relief.	None	Oral analgesics, NSAIDs, physical therapy, diagnostic xylocaine muscle block, joint aspiration (no fluid
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δ BONT/A: Botulinum toxin type A, φMAS: Modified Ashworth Scale, μ HHS: Harris Hip Score, *ROM: Range of Motion, ηVAS: Visual Analog Scale, αMRC: Medical Research Council, ¶ODI: Oswestry Disability Index,

Discussion

BoNT/A has gained increasing attention as a treatment option for managing chronic pain and flexion contractures following TKA and THA. This systematic review synthesizes the available evidence from randomized controlled trials and case studies evaluating its efficacy, dosing strategies, injection sites, and safety.

Pain Management and Functional Outcomes

In patients who had undergone TKA, WOMAC total scores improved significantly following BoNT/A injections.^{18,22} Singh et al.¹⁸ reported a trend toward reductions in VAS and WOMAC pain scores in the BoNT/A group, although these changes did not reach statistical significance. This may be attributed to heterogeneity in pain relief, higher baseline WOMAC pain scores in the placebo group, and the small sample size. However, clinically meaningful pain relief was observed, lasting a mean of 39 days after a 100 U intra-articular BoNT/A injection in patients more than 6 months after TKA. Notably, by 4 months, VAS pain scores in the placebo and BoNT/A groups had converged, suggesting that higher doses or repeated injections may be required to sustain clinically meaningful pain relief.

A subsequent study by Singh et al.²² administered intra-articular BoNT/A injections at an initial dose of 100 U, with escalation to 100–300 U in non-responders or patients with recurrent pain, in patients with persistent pain 1 year after TKA. They observed a significant reduction in daytime NRS pain scores that was maintained throughout follow-up, whereas nighttime NRS pain scores showed a non-significant trend, likely because of lower baseline nighttime pain scores. Importantly, 57% of patients reported a 50% reduction in daytime NRS pain at 3–4 months after injection, and this reduction persisted at subsequent 3–4- and 5–9-month follow-ups. However, the small sample size may limit the generalizability of these findings.

Regarding functional outcomes, KSS scores improved significantly in BoNT/A-treated patients in the studies by Vahedi et al.²⁰ and Seyler et al.,¹² although independent pain scores were not reported, limiting interpretation of pain-specific improvements.

In patients who had undergone THA, all studies reported reductions in pain scores following BoNT/A injections. Fish et al.²⁴ reported an improved ODI at 6 months, although pain scores worsened compared with earlier follow-up, potentially reflecting the transient analgesic effect of

BoNT/A. In addition, because the ODI primarily assesses disability related to low back pain, it may not fully capture improvements in hip function. More robust functional scales, such as the HHS, demonstrated more consistent and clinically meaningful improvements in the studies by Bhavet al.¹⁴ and Santamato et al.²³ Nonetheless, small sample sizes and procedural variability limit the generalizability of these findings.

Dosing Strategies and Muscle Targeting

In most TKA studies, 100 U of BoNT/A was administered either intra-articularly or into the hamstrings, with limited consideration of patient-specific factors such as BMI, except in the study by Cheesman et al.¹⁹ Intra-articular doses ranged from 100 to 300 U, whereas intramuscular doses varied from 100 to 400 U, with a maximum of 200 U per affected hamstring. Singh et al.²² explored different dosages but found no significant correlation between dose and either the duration of pain relief or the incidence of adverse events.

Comparisons of pain relief across different doses or injection sites were challenging, as the studies employed varying pain scales. However, functional outcomes, such as KSS scores, demonstrated a mean improvement of approximately 35 points in the studies by Vahedi et al.²⁰ and Seyler et al.¹² Vahedi et al.²⁰ administered 150–200 U to each gastrocnemius and hamstring muscle, whereas Seyler et al.¹² used 100 U in each hamstring and 50 U in the gastrocnemius. These findings suggest that lower BoNT/A doses may be similarly effective in improving overall functional scores, although differences in concomitant therapies may confound these results.

Overall, a dose of 100 U intra-articularly or 200–250 U intramuscularly (distributed across both hamstrings and/or gastrocnemius) appeared sufficient to achieve clinically meaningful outcomes. Nonetheless, further studies are needed to establish optimal dosing strategies and to clarify the influence of factors such as BMI.

In THA studies, BoNT/A doses ranged from 100 to 300 U per session, with target muscles selected according to individual contractures or pain patterns, including the adductors (50–150 U), iliopsoas (100–200 U), tensor fasciae latae (50–100 U), rectus femoris (100 U), and gluteus maximus (200 U). Significant improvements were observed even with doses as low as 100 U, suggesting a potential lower threshold for effectiveness. For instance, Fish et al.²⁴ reported worsening NRS pain scores 6 months after a 200 U injection into the

gluteus maximus, whereas Bertoni et al.¹¹ observed sustained pain reduction up to 16 months (VAS 0) following a 100 U injection into the iliopsoas. These contrasting findings highlight the need for further comparative studies to clarify dose–response relationships, optimal injection sites, and the potential need for repeated injections.

Optimal Time of Intervention

The interval between arthroplasty and BoNT/A injection varied widely (TKA: 18 days to 31 months; THA: preoperative to 1 year postoperative). Positive outcomes were reported across this range, suggesting a broad therapeutic window. Patients treated within 3 months postoperatively often showed limited progress with standard therapies during the first 6–7 weeks. Some studies did not specify the rationale behind timing decisions. Notably, BoNT/A dosage did not increase with longer intervals between surgery and injection. Mitsuyasu et al.²⁵ reported that persistent flexion contractures lasting beyond 3 months were unlikely to resolve spontaneously. Before 3 months, pain is predominantly attributable to surgical trauma, inflammation, and healing processes, with muscle spasms often resolving with physical therapy. Beyond 3 months, residual pain is less likely due to acute inflammation and more likely related to chronic contractures or persistent dysfunction.^{26,27}

In summary, BoNT/A injections were generally considered for patients with contractures persisting beyond 3 months post-TKA, or for those with chronic pain unresponsive to standard rehabilitation and orthoses, typically 6 months to 1 year post-TKA. In non-spastic patients, injections were administered between 1 month and 1 year postoperatively, often prompted by lack of progress in rehabilitation and a positive response to diagnostic nerve blocks with local anesthetic. Controlled trials with homogeneous patient populations are needed to define the optimal timing, dosing, and injection sites for BoNT/A administration. However, spasticity-related cases, such as those described by Frost et al.⁴ and Eibach et al.,¹³ may limit the applicability of these results to the general arthroplasty population. In these spastic patients, preoperative BoNT/A injection was often used as a preventive strategy. This represents a distinct clinical indication and patient population compared with the general arthroplasty population. Although both settings involve BoNT/A and joint surgery, the underlying pathophysiology, treatment goals, and outcomes differ significantly. Therefore, findings from preoperative studies should not be directly extrapolated to postoperative cases, and future research should consider these distinctions when designing clinical trials.

Efficacy in Range of Motion

TKA studies demonstrated mixed results. BoNT/A injections led to improvements in knee extension and overall ROM, although not all studies reported statistically significant changes. For example, Smith et al.¹⁰ observed significant gains in knee extension at 12 months, but no statistically significant improvement in overall ROM compared with controls. Conversely, Seyler et al.¹² reported

significant ROM gains; however, the absence of a control group limits interpretation. Small sample sizes and baseline variability likely contributed to these inconsistent findings.

In THA patients, results were more consistent, with all studies reporting improved hip mobility through reductions in flexion contractures. Eibach et al.¹³ and Bhavé et al.¹⁴ documented decreases in contracture angles of 25° and 23°, respectively. Nevertheless, these findings were primarily derived from case reports with limited statistical analysis, underscoring the need for controlled studies.

Safety and Tolerability

Across the reviewed studies, BoNT/A demonstrated a favorable safety profile, even at maximum doses of up to 400 U per session. No serious adverse events were directly attributed to treatment. The most commonly reported mild adverse events included bruising, localized pain, muscle weakness, headache, flu-like symptoms, and swelling. Notably, these adverse events occurred at similar rates in both the BoNT/A and control groups.

For example, Vahedi et al.²⁰ administered doses of up to 200 U without observing any complications. In addition, evidence suggests that neither higher doses nor repeated BoNT/A injections significantly increased the incidence of adverse effects.²² These findings support the relative safety of BoNT/A injections as a therapeutic option for managing pain following arthroplasty.

Transient muscle weakness, a well-documented effect of BoNT/A related to its neuromuscular blocking action, deserves particular attention in the context of joint arthroplasty.^{6,7} In patients recovering from TKA or THA, residual muscle weakness, particularly in key stabilizing muscles such as the hamstrings, gastrocnemius, iliopsoas, or adductors, could potentially impair functional recovery, delay rehabilitation, or increase fall risk.^{7,28} Although the studies included in this review reported only mild and transient weakness,¹¹ the lack of standardized assessment tools, such as objective strength testing using the MRC scale or dynamometry, limits the ability to quantify this risk. Therefore, although BoNT/A appears safe overall, the potential for clinically meaningful muscle weakness should be carefully weighed against its benefits, especially in patients with limited functional reserve.

Limitations and Strengths

This review has several important limitations that should be considered when interpreting its findings. A major limitation is the frequent use of concomitant therapies alongside BoNT/A, including anti-inflammatory medications, physical therapy, braces, manipulation under anesthesia, tenotomies, and nerve decompression. This makes it difficult to isolate the specific therapeutic effect of BoNT/A, as improvements in pain and function may reflect synergistic effects or the cumulative impact of multiple interventions. For instance, a patient receiving BoNT/A followed by aggressive stretching and MUA may show improved knee extension; however, it remains unclear whether this improvement is attributable to muscle relaxation, mechanical effects, or therapeutic synergy. The timing and intensity of adjunctive therapies

varied substantially across studies, with some administered before, after, or concurrently with BoNT/A, further complicating cross-study comparisons and reducing confidence in conclusions regarding the independent efficacy of BoNT/A. In addition, most included studies were small case series or case reports, limiting statistical power and generalizability. Many studies lacked control groups or failed to report key statistical measures, such as p-values, reducing the ability to assess true treatment effects. Variability in BoNT/A doses, ranging from 50 to 300 U, and injection sites also makes it challenging to determine optimal treatment protocols. Moreover, inconsistent outcome measures, including different pain and functional scales such as the HHS, ODI, NRS, WOMAC, and VAS, hinder meaningful comparisons and preclude meta-analytic synthesis. The exclusion of non-English-language studies may also have introduced language bias. This decision was primarily driven by practical constraints, including the availability of translation services and the need to ensure consistent quality assessment across all included studies.

Despite these limitations, this review has several notable strengths. It represents the first systematic examination of all available primary literature on BoNT/A for pain and contracture management following total knee and hip arthroplasty, providing a broad and comprehensive overview of its clinical applications. The inclusion of randomized controlled trials, although limited in number, strengthens the evidence base and provides a more rigorous foundation for evaluating both efficacy and safety. This review also provides a detailed assessment of adverse events, including those associated with repeated injections and higher doses, offering valuable insights into the tolerability and risk profile of BoNT/A in this patient population. Furthermore, by incorporating diverse study designs, this review identifies important research gaps, including optimal injection timing, site-specific effectiveness, and dose-response relationships, thereby providing a clear framework for future clinical trials and more targeted, evidence-based treatment strategies.

Clinical Considerations and Preliminary Recommendations

Based on the reviewed evidence, it is premature to endorse standardized BoNT/A protocols for routine clinical use in post-arthroplasty complications. Variability in study designs, dosing regimens, and outcome measures precludes the formulation of definitive clinical guidelines. Nevertheless, for clinicians considering BoNT/A as an adjunctive therapy, the following considerations are recommended:

1. Absence of Standardized Protocols

Clinicians should recognize that there is currently no established “gold standard” for BoNT/A dosing, timing, or injection site selection. The wide range of reported doses (50–400 U) and variable intervals from preoperative to 31 months postoperative reflect a lack of consensus. Accordingly, BoNT/A should be considered an adjunctive, off-label intervention for patients who have not responded to conventional conservative management, such as intensive physical therapy, MUA, or pharmacological therapy.

2. Timing of Intervention

Evidence suggests that BoNT/A is most appropriate when symptoms persist beyond the acute recovery phase.

Post-3 Months: During the first 12 weeks following TKA or THA, pain and stiffness are often driven by acute inflammation and surgical trauma. BoNT/A intervention is generally recommended only after this period, once it is clear that muscle hypertonicity or chronic pain sensitization—rather than acute healing processes—is the primary contributor to dysfunction.

Exception for Spasticity: In patients with established neurological spasticity (e.g., cerebral palsy or stroke), earlier or even preoperative BoNT/A intervention may be warranted to prevent the development of severe postoperative contractures.

3. Individualized Dosing and Patient Factors

Dosing should not be arbitrary but should instead be tailored to the patient’s physiological profile.

Muscle Mass and BMI: Patients with greater muscle mass or higher BMI may require higher doses, approaching 300–400 U, or ultrasound/electromyography (EMG) guidance to ensure accurate delivery to deep muscle groups, such as the iliopsoas or the short head of the hamstrings. Conversely, in elderly patients with substantial muscle atrophy, lower doses may be advisable to minimize the risk of clinically significant muscle weakness.

Severity of Contracture: For mild flexion contractures (<15°), lower doses targeting a single muscle group, such as the hamstrings, may be sufficient. For multiplanar stiffness or severe contractures, a multi-site approach involving both the hamstrings and gastrocnemius may be necessary.

4. Safety-First Approach to Muscle Weakness

Given the importance of muscle strength for post-arthroplasty stability, clinicians should adopt a “start low, go slow” approach. Initiating treatment at the lower end of the reported dosing range (e.g., 100 U) allows clinicians to assess the patient’s sensitivity and the functional impact of muscle relaxation before considering dose escalation in subsequent sessions.

5. Combined Therapy Framework

BoNT/A should not be used as a standalone treatment. Its primary value lies in creating a “therapeutic window” of reduced pain and muscle hypertonicity. Clinicians should ensure that injections are followed immediately by an intensified, structured physical therapy program to maximize gains in range of motion while the neurotoxin is active, typically for 3–4 months.

Conclusion

BoNT/A injections appear to be safe and potentially effective for managing chronic pain after TKA and THA. Painful TKA is primarily managed with intra-articular injections, whereas intramuscular injections are used to target flexion contractures. Most studies reported pain relief and improved joint function with doses ranging from 100 to 400 U, with no serious adverse events. However, the

potential for transient muscle weakness, particularly in patients undergoing rehabilitation, should be explicitly discussed with patients and incorporated into clinical decision-making.

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