REVIEW ARTICLE

The Efficacy of Botulinum Toxin in the Management of Restless Leg Syndrome: A Systematic Review of Randomized Control Trials

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Abstract

Background: Restless legs syndrome (RLS) is a sleep-related movement disorder characterized by an irresistible urge to move the legs, occasionally associated with unpleasant sensations in the leg. Emerging evidence suggests that botulinum neurotoxin may be effective in reducing the symptoms of RLS.

Objective: The objective of the present review was to assess the effectiveness of botulinum toxin in patients with RLS.

Methods: The focused question was "Is botulinum neurotoxin effective in reducing the severity of RLS?" Using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) model, indexed databases were searched up to and including February 2021. Joanna Brigg's critical appraisal tool was used to evaluate the risk of bias (ROB) for the included studies.

Result: Four clinical studies were included in the systematic review and processed for data extraction. Three studies reported that the botulinum neurotoxin type A (BoNT/A) had an impact in reducing the severity and improving RLS. One study reported that BoNT/A provides no effectiveness in managing RLS. Overall risk of bias was low in two and moderate in two studies.

Conclusion: The present review suggests the need of more robust high-quality evidence for recommending the management of RLS with BoNT/A on reducing the severity and improving the overall symptoms of RLS.

Keywords: Botox, Botulinum, Pain, Restless leg syndrome, Toxin.

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Introduction

Restless legs syndrome (RLS) is a sensorimotor neurological disorder characterized by an irrepressible urge to move the legs and occasionally associated with paresthesia and pain. The symptoms are typically aggravated with rest, especially at night and often relieved by movement. The International Classification of Sleep Disorders (ICHD-3) classifies RLS as a sleep-related movement disorder. The estimated prevalence ranges from 1 to 10%, with a female predilection[1,2] and commonly affects people in the third to eighth decade of life.[3] The worldwide prevalence is estimated to be 1.9–4.6%, while in the United States of America, it is estimated to be 5–8.8% of the adult population.[4] Comorbid conditions in RLS may include but not limited to parkinsonism, rheumatoid arthritis, peripheral neuropathy, acting out dreams, hyposmia, cardio-metabolic risk factors, fibromyalgia, depression, and anxiety disorders.[5] There are two types of RLS, idiopathic or secondary RLS.[6] The pathophysiology of RLS is not fully understood, but it has been proposed that RLS may be generated by dopamine dysfunction within the central nervous system (CNS). Emerging evidence proposes the role of impaired cortical sensorimotor integration,[2] hyper excitability in the cortical-striatal-thalamic-cortical network producing hyper excitability of the spinal motor neurons as possible pathophysiological mechanisms in the genesis of RLS.[7,8]

The management of RLS can vary and includes nonpharma cological and pharmacological treatments. Nonpharmacological management includes repetitive transcranial magnetic stimulation, infrared therapy, compression devices, exercise, counterstain manipulation, and acupuncture.[9] The pharmacologic treatment can include dopamine agonists, α-2-δ calcium-channel ligands, tricyclic antidepressants, clonazepam, opioids, and iron supplementation or injections.[8,10,11] In addition, treatment with dopaminergic agonists for long durations may increase the risk of worsening of symptoms of RLS, a phenomenon which is referred to as augmentation.[1,12,13]

Several studies and case series have shown encouraging results in terms of effectiveness of BoNT in reducing the severity of RLS. Subsequently some of the clinical trials were published. A study done by Mittal et al. showed significant improvement in pain scores in patients who received BoNT/A for the management of RLS.[1] In

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contrast, another study showed no efficacy of BoNT/A in alleviating RLS sensory symptoms.[8] A study done by Nahab et al. compared the effect of BoNT/A and placebo showed no improvement up to week 12 post injection,[2] whereas another study reported an improvement in RLS during the first 4 weeks following BoNT/A administration.[14] Due to the absence of clear evidence based on the current data, the present review was performed to systematically review the literature on the efficacy of BoNT in the management of patients with RLS.

Materials and Methods

This systematic review was conducted in accordance with the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[15] The study was registered with PROSPERO (CRD42021261045). Due to high heterogeneity in the studies, a meta-analysis was not performed.

Focused Question

The addressed focus question was "Is botulinum neurotoxin effective in reducing the severity of RLS?"

Population, Intervention, Control, Outcome (PICO)

The Population, Intervention, Control, and Outcome (P = patient with RLS; I = BoNT therapy; C = other treatments or no treatment; O = improvement in severity of RLS).

Eligibility Criteria

The eligibility criteria were as follows: (a) clinical studies; (b) patients diagnosed with RLS; (c) the presence of a control group without botulinum neurotoxin type therapy; and (d) the presence of experimental group with BoNT therapy. (e) Articles published in English. The excluded articles included the case reports, case-series, letters to the editor, commentaries, reviews, experimental studies, and cross-sectional studies.

Study Selection and Literature Search Protocol

An electronic search was conducted of indexed databases PubMed, EMBASE, Scopus, ISI Web of Knowledge, Cochrane library without time restriction up to and including February 2021, based on the "Preferred Reporting Items for Systematic Review and Meta-analysis" (PRISMA) guidelines.[15] The following keywords were used: (1) restless legs syndrome; (2) botulinum neurotoxin type A; (3) botulinum toxin; (4) incobotulinum toxin A; and (5) movement disorder. To expand the search results, these keywords were combined using Boolean operators (OR, AND).

Screening Methods, Data Extraction, and Risk of Bias Assessment

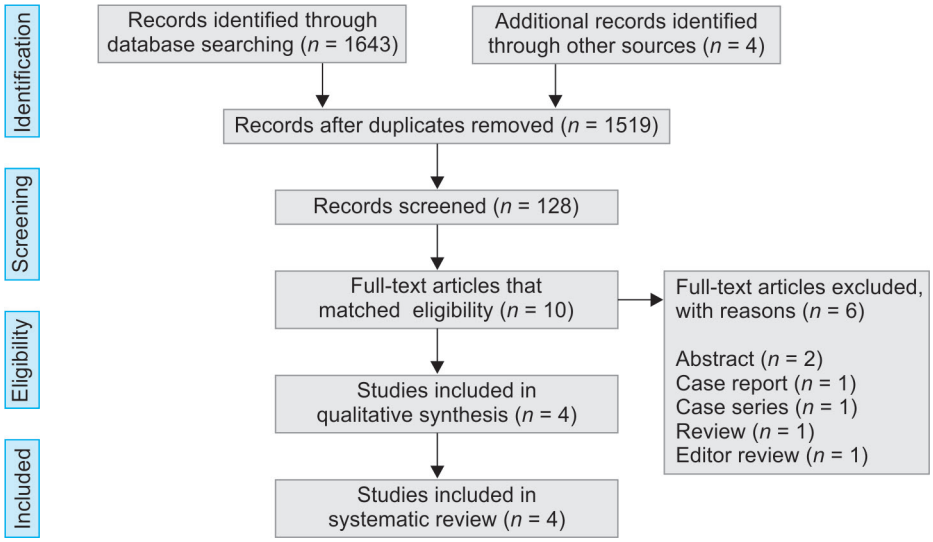
The articles were reviewed by two authors (MA, ST) independently, by screening the titles and abstracts of 128 identified studies. Studies that were not relevant to the current study, duplicates, or did not have the focused question were excluded. Disagreements were solved through mutual discussion between reviewers, and in case of a lack of consensus through discussion, a third reviewer (JK) was involved. The search strategy has been detailed in Flowchart 1. All the information from the included studies were synthesized by tabulating the data according to (a) study design, (b) the characteristics about BoNT/A administration, (c) relevance of study characteristics of participants with RLS, (d) duration of the follow-up treatments, (e) study outcomes of BoNT/A administration on patients with RLS. A quality assessment was performed. The risk of bias of the included studies was assessed using the Joanna Brigg's Institute (JBI) assessment. The JBI assessment tool is used to assess the quality and evaluates the study design, methodology, conduct, and analysis of a study for bias Studies included qualitative and quantitative assessment based upon the Preferred Reporting Items for Systematic Review.

Results

General Characteristics of Included Studies

The initial search generated 1,647 studies, and 1,519 articles were excluded after removal of duplicates. After title and abstract screening, 118 studies were excluded based on eligibility criteria. Full-texts of 10 studies were initially assessed for eligibility out of which 6 studies were excluded [abstracts $n = 2$, case reports ($n = 1$), case series ($n = 1$), review ($n = 1$), editor review ($n = 1$)]. Finally, four randomized clinical studies were included in the systematic review and processed for data extraction (Flowchart 1). The total number of participants in studies ranged from 6 to 27 subjects. The mean

Flowchart 1: PRISMA flowchart for literature search



age in the four studies was 57.6 ± 14.3 years old. Only three studies reported male and female participants. The follow-up of the patients ranged from the first week following BoNT/A administration and up to 2 years. Some of the participants were excluded from the study for numerous reasons, including negative side effects, death, and patients who did not complete the follow-up appointments[1,2,8,14] (Table 1). In the study by Ghorayeb et al., of the 27 included patients, 26 completed the full 6-month trial. One patient withdrew from the study after completing the week 12 visit. The reason for withdrawal was a lack of efficacy of BoNT/A and the need to rapidly proceed to RLS treatment modification. For this patient, data were collected for weeks 2, 6, and 12.[8] In the study by Nahab et al., seven patients were initially screened, with one excluded due to leukocytosis on serological testing. All remaining patients completed the study.[2]

General Characteristics of BoNT

The three types of BoNT A used in these studies were incobotulinumtoxinA (IncoA), abobotulinum toxin A (Abo A), and onabotulinum toxin A (OnaNT A) to treat RLS (Table 2). The severity of RLS ranged from moderate to severe. The mean dosage BoNT/A ranged from 50 to 1,000 units depending on the formulation used. There was a difference in the method of injections in these studies. While the study by Imad et al., Mittal et al., and Aggarwal et al. used intramuscular injections, Nahab et al. used intradermal injections spread over a wide area in the legs. The number of injections sites varied and involved the quadriceps femoris, tibialis anterior, gastrocnemius, soleus muscles, and intradermal injections in anterior and posterior thighs and legs. Moreover, the duration of the treatment ranged from every 2 weeks for up to 6 months. In one study, BoNT/A was given in combination with other treatments like opioids, analgesic/anti-inflammatory, anticonvulsant, antidepressant, dopamine agonist, and clonazepam.[8]

General Characteristics of Outcome

The outcome measurement was evaluated using the International Restless Legs Syndrome Scale (IRLS), Visual Analog Scale (VAS), Johns Hopkins Quality of Life Questionnaire (JHQOL), Clinical Global Impression Improvement (GGII), Efficacy Duration, Patients' Global Impression of Severity of Illness, and Epworth Sleepiness Scale (ESS).

In the study by Mittal et al., there was a significant improvement from a severe (IRLS >21) to a mild/moderate (IRLS ≤20) score at 4 and 6 weeks, but no significant improvement was detected at 8 weeks post administration of BoNT. Additionally, there was a significant improvement in pain scores at 4 weeks and in the JH QoL questionnaire at 6 weeks in the IncoA group.[1] A marked improvement on patient global impression of change was seen in 7 out of 21 patients in the IncoA group vs. 1 out of 21 patients in the placebo group at 4 weeks.

In the study by Agarwal et al., IRLS scores at visit 2 showed an improvement in RLS score. There was a statistically significant difference in PGI-S between initial visit and visit 3. There was no difference found in clinical assessment of disease severity as indicated by CGI-S between initial visit and visit 3.[14]

In the study by Ghorayeb et al., BoNT/A improved the average IRLS score of the entire group. The mean RLS severity baseline score significantly dropped at week 2 and lasted for up to week 24.[8]

In the study by Nahab et al., at week 4, BTX-treated patients showed significant improvement in the IRLS score. The CGI showed similar findings at week 4.[2] Overall, the treatment with both onabtuulinum toxin A, abobotulinum toxin A, and incobotulinum toxin A showed improvement in pain and reduced RLS severity in

Table 1: General characteristics of included studies

Author	*Year published*	*Study design/type of BoNT used*	*Number of subjects Male/female*	*Mean age ± SD (years)*	*Subjects in the test group*	*Responder to the treatment*	*Subjects in the placebo group*	*Non-responders to the treatment*	*Cross-over*
Mittal et al.[1]	2018	Randomized double-blind placebo-controlled crossover/ (incobotulinum toxin)	Total *n* = 21 Males = 10 Females = 11	60.5 ± 13.49	8	NR	13	NR	Yes
Ghorayeb et al.[8]	2012	Noncomparative clinical trial (abobotulinum toxin)	Total *n* = 27 Males = 15 Females = 12	57.6 ± 14.3	NR	6	NR	21	NR
Nahab et al.[2]	2008	Randomized a double-blind placebo-controlled trial (onabotulinum toxin)	Total *n* = 6 Males = 3 Females = 3	57.7 ± 8.8	3	NR	3	NR	NR
Agarwal et al.[14]	2011	Randomized control trial, a single-arm, open-label pilot trial (onabotulinum toxin)	Total *n* = 8 Not reported	62.75 ± 8.8	8	NR	NR	NR	NR

NR, not reported; BoNT/A, botulinum neurotoxin type A; SD, standard deviation

Table 2: General characteristics of botulinum toxin type A

Author	*Type of BoNT*	*Provider who injected*	*EMG-guided injections*	*Needle gauge*	*Mean number of injections*	*Mean dosage of BoNT/A in units*	*Type of injection*	*Location of injections*	*Right, or left or both legs*	*Severity of RLS*	*Duration of RLS (mean ± SD)*	*Previous treatments*	*Medication at time of BTX-A injection*	*Duration of treatment*
Mittal et al.[1]	Incobotulinumtoxin A (IncoA) ®Xeomin	Neurologist	Yes	A 27	NR	200	NR	Quadriceps femoris, anterior tibialis, Gastrocnemius, Soleus muscles.	Both	Moderate–Severe	NR	NR	NR	(4, 6, and 8) weeks intervals for 12 weeks.
Ghorayeb et al.[8]	Abobotulinum toxinA-®Dysport	NR	NR	NR	20	500–1,000	Intradermal injections	Anterior and posterior thighs and legs.	Both	Severe	31.1 ± 4.7	NR	Weak analgesics/anti-inflammatory. Opioid analgesics. Antidepressants. Antiepileptic. Hypnotics.	(2, 6, 12, 18 and 24) weeks intervals for 6 months.
Nahab et al.[2]	Onabotulinum toxin (®Botox)	NR	Yes	NR	2–4	90	Intramuscular	Quadriceps femoris, Tibialis anterior, Gastrocnemius, Soleus muscles.	NR	Moderate–Severe	33.5 ± 14.4 years	Dopamine agonist Clonazepam (6 weeks)	Dopamine agonist Clonazepam	(2 and 4) weeks post-injections for 12 weeks.
Agarwal et al.[14]	Onabotulinum toxin A (®Botox)	NR	NR	NR	2	50	Intramuscular	Tibialis anterior muscles.	Both	Moderate–Severe primary RLS	NR	NR	NR	Follow-up 4 weeks and 12 weeks.

NR, not reported; EMG, electromyography

three studies. At the same time, one study showed no improvement in RLS symptoms. However, some patients showed different adverse effects like leukocytosis, diplopia, moderate transient limb, and weakness in legs. The sample size and statistical analysis were performed in all studies. Three studies showed significant improvement of RLS with BoNT/A treatment. While only one study showed that it was ineffective or there was no improvement with the treatment (Table 3).

Risk of Bias

The risk of bias of included studies was assessed by two authors using the JBI critical appraisal checklist for a randomized control trial. This has been depicted in Figure 1. In two of the studies, all the participants and the examiner were blinded to treatment and treatment assignments. In one study, participants were not blinded to the treatment and procedure; it is unclear if the provider or the outcome assessors were blinded. Follow-up visits were mentioned in all four studies, and if the patient did not complete, the reasons were mentioned. The risk of bias of included studies was assessed by two authors MA and ST using Joanna Brigg's Risk of bias assessment tool for randomized control trials (Table 4). A total of 13 questions were used to evaluate overall quality of the included studies. The overall ROB was low for two studies[1,2] and moderate for two studies.[8,14] All the four studies used true randomization for the assignment of patient to different treatment groups.[1,2,8,14] Allocation to treatment groups was concealed in two studies[1,2] and not concealed in one study[8] and was unclear in one study.[14] All studies recruited patients similar at the baseline.[1,2,8,14] Blinding of participants was done in two studies[1,2] and is not done in two other studies.[8,14] Blinding of those delivering treatment to treatment assignments was fulfilled in two studies,[1,2] was not done in one study,[14] and unclear in one study.[8] Blinding of outcome assessors was done in three studies[1,2,14] and unclear in one study.[8] Treatment of groups other than intervention of interest was reported in three studies[1,2,8] and was not applicable in one study.[14] Completion of follow-up and reporting of attrition were done in all the four studies.[1,2,8,14] Analysis of the participants to the groups they were randomized was fulfilled in three studies[1,8,14] and unclear in one study.[2] Measurement of outcomes was similar in all the four studies.[1,2,8,14] Measurement of outcomes was reliable is all of the studies.[1,2,8,14] Appropriate statistical analysis was used in all studies.[1,2,8,14] Trial design was appropriate in all the four studies.[1,2,8,14]

Discussion

BoNT has been used in healthcare to manage conditions such as movement disorders, spasticity, myofascial pain, headache disorders such as migraine, dystonia's, strabismus, upper or lower limb spasticity, overactive bladder, urinary incontinence, severe axillary hyperhidrosis, and cosmetic procedures. RLS is a common neurological sensory-motor disorder identified by unpleasant sensations in the lower leg. Symptoms are worse at night, often interfering with sleep that can negatively affect the patient's daily activities and overall quality of life.[6,16]

BoNTs are produced by different strains of clostridium botulinum bacteria. There are seven common types of botulinum toxins that have been identified (A, B, C, D, E, F, G).[1,17] BoNTs types A and B are commercially available and predominantly utilized in clinical settings. However, there are several subtypes that have been identified for each toxin type (subtypes A1, A2, A3).[1,17] Botulinum

Table 3: General characteristics of outcome variables

Author	*Adverse of treatment*	*Parameter assessed*	*Result*	*Duration of follow-up*	*p value*	*Outcome*
Mittal et al.[1]	Not reported	International RLS score (IRLS) Visual analog scale (VAS) Johns Hopkins quality of life questionnaire (JHQLQ)	Improvement Improvement Improvement Improvement	12 weeks	$p < 0.05$	IncoA injection led to a reduction in severity of RLS symptoms, pain score, and quality of life, without any adverse effects.
Ghorayeb et al.[8]	Moderate transient limb weakness. Transient diplopia	RLS severity score Clinical global impression-improvement (CGI-I)	Improvement Improvement	24 weeks	$p < 0.05$	No efficacy in alleviating RLS sensory symptoms after BoNT/A injection.
Nahab et al.[2]	Leukocytosis	International RLS score (IRLS) Clinical global impression-improvement (CGI-I)	No Improvement No Improvement	12 weeks	$p > 0.05$	No efficacy of treatment.
Agarwal et al.[14]	Not reported	International RLS score (IRLS) Visual analog scale (VAS) Patients' global impression of change (PGIC) Epworth sleepiness scale (ESS)	Improvement Improvement Improvement Improvement	12 weeks	$p < 0.05$	Effective and safe.

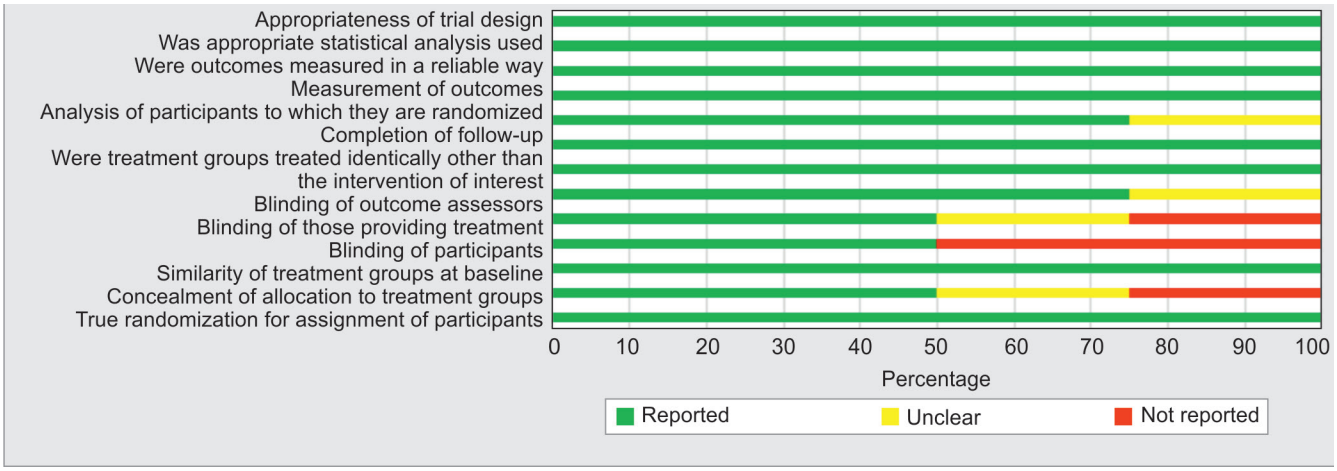


Fig. 1: Figure depicting risk of bias

Table 4: Risk of bias of the included randomized controlled clinical trials

Domain	*Mitta et al.*[1]	*Ghorayeb et al.*[8]	*Nahab et al.*[2]	*Agarwal et al.*[14]
1	Yes	Yes	Yes	Yes
2	Yes	No	Yes	Unclear
3	Yes	Yes	Yes	Yes
4	Yes	No	Yes	No
5	Yes	Unclear	Yes	No
6	Yes	Unclear	Yes	Yes
7	Yes	Yes	Yes	NA
8	Yes	Yes	Yes	Yes
9	Yes	Yes	Unclear	Yes
10	Yes	Yes	Yes	Yes
11	Yes	Yes	Yes	Yes
12	Yes	Yes	Yes	Yes
13	Yes	Yes	Yes	No
Summary	Yes	Yes	Yes	Yes
Overall risk of bias	Low	Moderate	Low	Moderate

1. Was true randomization used for assignment of participants to treatment groups?
2. Was allocation to treatment groups concealed?
3. Were treatment groups similar at the baseline?
4. Were participants blind to treatment assignment?
5. Were those delivering treatment blind to treatment assignment?
6. Were outcomes assessors blind to treatment assignment?
7. Were treatment groups treated identically other than the intervention of interest?
8. Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analyzed?
9. Were participants analyzed in the groups to which they were randomized?
10. Were outcomes measured in the same way for treatment groups?
11. Were outcomes measured in a reliable way?
12. Was appropriate statistical analysis used?
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

neurotoxin type A (BoNT/A) has been used in the management of various conditions such as myofascial pain, bruxism, migraines, dystonia's, strabismus, upper or lower limb spasticity, overactive bladder, urinary incontinence, and severe axillary hyperhidrosis. Injection of botulinum neurotoxins (BoNTs) into the muscles or skin of patients with RLS may help reduce increased sensitivity and thus offer beneficial effects.[1] Although precise mechanisms of BoNT/A in nociception are still unclear, it has been suggested to inhibit transduction process in nociceptors. BoNT may have a more specific effect on mechanotransduction. BoNT/A may alter the expression of mechanically gated currents in neurons. Transient receptor potential (TRP) plays a significant role in nociception and is increasingly being explored as therapeutic channels for pharmacologic management of chronic pain. BoNT may additionally play a role in modulating the expression, translocation, and function of TRP channels in nociceptors and thus play a role in the management of RLS symptoms.[18,19] BoNT/A works primarily by cleavage of soluble N-ethylmaleimide-sensitive fusion protein attachment receptor (SNARE) proteins located at synaptic terminals of the neuromuscular junction. Cleavage of SNARE proteins prevents release of acetylcholine (Ach), and the clinical result is muscle weakness.[2] The continued blockage of Ach in the neuromuscular junction by BoNT/A can lead to chemo denervation, which is one of the proposed mechanisms of action for BoNT/A used in the management of RLS, cervical dystonia, blepharospasm, hemifacial spasm, spasticity, tremor, and other neurological disorders.[1,8] The success rates however vary, and inconsistent therapeutic results are often reported. Overall, most of the studies performed show a positive effect of BoNT/A, at least in the short term and some neurological conditions may require additional injections at follow-up.

Presently, treatment options for idiopathic RLS include pharmacotherapy, and iron supplements depending on the etiology as being primary RLS or secondary RLS. In this review, four clinical trials were included to evaluate the efficacy of BoNT in the management of patients with RLS. The studies included patients who were 18 years and older; both males and females were included and the severity of the RLS reported ranged from moderate to very severe. Some of the participants were taking

medications in addition to the management with BoNT/A. These medications included nonsteroidal anti-inflammatory, opioids, antidepressants, antiepileptics, dopamine agonists, and hypnotics. Both legs were injected in muscles that included quadriceps femoris, tibialis anterior, gastrocnemius, soleus muscles, and intradermal injections in anterior and posterior thighs and legs. The mean dosage of BoNT/A ranged from 50 to 1,000 units depending on the formulation used. Some of the patients developed adverse effects like leukocytosis, diplopia, moderate transient limb, and weakness in legs.

Overall, three out of four studies showed that the BoNT improved the severity symptoms of RLS. Both BoNT/A and OBoNT/A were effective in managing primary RLS instead of medication or in combination with medication for severe cases. Pharmacotherapeutic management for extended time may increase the risk adverse side effects like drowsiness, headache, dry mouth, nausea, vomiting, constipation, movement-related problems (dyskinesia), fainting, sudden sleepiness, swelling of legs, behavior alterations, and also produce augmentation.[1]

The limitations of the review include the nonuniform methodology followed in the trials as well as the variability in injections technique, botulinum toxinA formulation, doses, and low sample size. Furthermore, various types of BoNT were reported to be used. The outcome variables were not consistent and the injection regimen and duration were not homogeneous. From a clinical perspective, the above-mentioned factors can influence the overall outcome of management. Future studies should emphasize on generalizability, sample size analysis, and standardized assessment of outcomes.

Conclusion

Limited studies with low sample size on the treatment with different types of BontA on symptoms of RLS show that there is relief and improvement of RLS symptoms. However, larger studies and randomized clinical trials are needed to improve the quality of evidence.

Author Roles

- Research project: A. Conception, B. Organization, C. Execution;
- Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
- Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

Ethical Compliance Statement

All submissions, regardless of type, require an Ethical Compliance Statement at the end of the manuscript. This must include all three of the following:

- The systematic review was registered at PROSPERO database.
- Declaration of patient consent—"Informed patient consent was not necessary for this work."
- "We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines."

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