Therapeutic Utility of Pyridostigmine for Distant Botulinum Dissemination Following Cervicofacial Injection: A Systematic Review

WAYNE STATE
School of Medicine

Anagha Srivatsa BS[1], Louie Mekani BS[1], Andrew J. Stefan MD[2], Michael A. Carron MD[2]
[1]Wayne State University School of Medicine, Detroit, MI, USA.
[2]Department of Otolaryngology, Wayne State University, Detroit, MI, USA.

Introduction

- Cervicofacial injection of botulinum toxin is widely used for cosmetic and non-cosmetic indications
- Examples include rhytides, sialorrhea, spasmodic dysphonia, and cricopharyngeal dysfunction
- Rarely, systemic absorption of botulinum toxin can result in adverse effects due to extraneous dissemination
- Examples include:
  - ptosis
  - dysphagia
  - muscular weakness
  - dyspnea
- This systematic review aims to investigate clinical characteristics and outcomes of patients treated with pyridostigmine, an acetylcholinesterase inhibitor, for distant botulinum dissemination following cervicofacial injection.

Methods

- PubMed, Embase, Cochrane, and Scopus databases were searched for studies describing pyridostigmine use in botulinum toxicity
- Of 472 articles screened, 15 met inclusion criteria

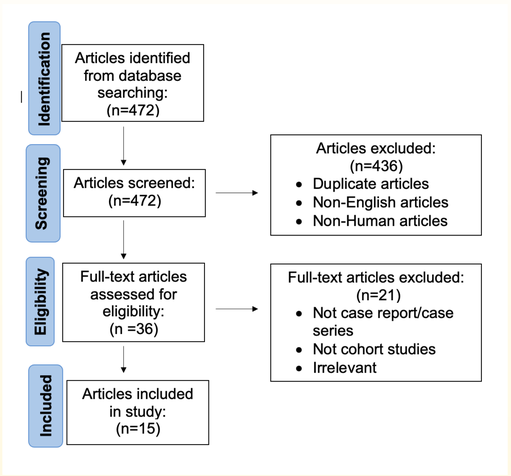


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Diagram

Results

- Thirty-one patients were included with mean age 47.8 years; 17 were female, 4 were male, and 10 unreported
- Indications for botulinum injection included adductor spasmodic dysphonia (41.9%), cosmesis (35.5%), and sialorrhea (6.5%)
- Common toxicity symptoms were dysphagia (45.2%), ptosis (25.8%), and generalized weakness (22.6%)
- After pyridostigmine initiation, 30 patients had improved symptoms after a mean of 6.1 days, with 3 patients reporting immediate benefit after administration
- Of note, 4 partial responders required adjunct antitoxin
- One patient developed asymptomatic bradycardia during pyridostigmine treatment

No. of Subjects	31
Mean Age (years), n (range)	47.8 (1-77)
Reported Male, n (%)	17 (54.8)
Reported Female, n (%)	4 (12.9)
Sex Unreported, n (%)	10 (32.3)
Mean Botulinum Dosage (U)	61.4 ± 125.9
Mean Time to Improvement, (days)	6.1 ± 8.9
Mean Pyridostigmine Treatment Duration, (days)	35.1 ± 47.4
Concomitant Therapies	
Antitoxin, n (%)	4 (12.9)
Other, n (%)*	2 (6.5)

*Methimazole, Tacrolimus

Table 1: Overview of Patients with Distant Botulinum Dissemination Treated with Pyridostigmine

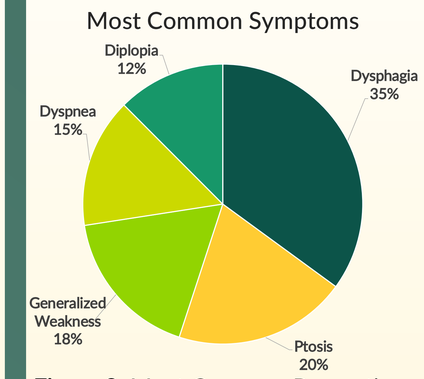


Figure 2: Most Common Presenting Symptoms For Patients with Botulinum Dissemination

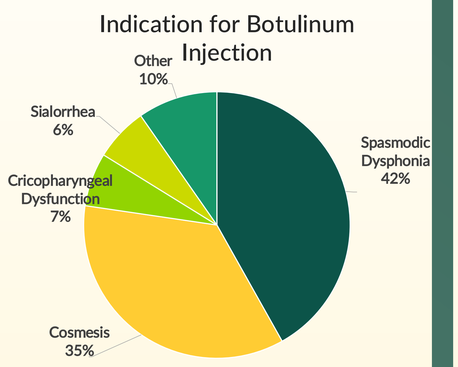


Figure 3: Most Common Indications for Botulinum Injection

Discussion

- In 2 patients, botulinum injected unmasked myasthenic gravis with neuromuscular symptoms improving with pyridostigmine
- Pyridostigmine has limited utility in true myasthenic crisis and should not be considered a substitute for standard crisis management
- One patient developed asymptomatic bradycardia during pyridostigmine treatment after dysphagia had resolved; discontinuation of pyridostigmine resulted in resolution of bradycardia
- Patients requiring antitoxin for incomplete response to pyridostigmine had received higher doses of botulinum toxin (>300 U)
  - This suggests a potential upper limit of botulinum toxin dosing, above which pyridostigmine may be less effective

Conclusion

- Pyridostigmine may offer an effective treatment for distant botulinum dissemination following cervicofacial injection
- Pyridostigmine was generally well tolerated, with one patient developing asymptomatic bradycardia that resolved following drug discontinuation
- Limitations include heterogeneity in reported data and variation in pyridostigmine treatment regimens
- Further research is needed to establish evidence-based criteria for patient selection, antitoxin escalation, and algorithmic pyridostigmine management

References

1. Watson NA, Siddiqui Z, Miller BJ, Karagama Y, Gibbins N. Non-aesthetic uses of botulinum toxin in the head and neck. *Eur Arch Otorhinolaryngol.* 2021;278(11):4147-4154. doi:10.1007/s00405-021-06750-4.
2. Lim M, Mace A, Nouraei SAR, Sandhu G. Botulinum toxin in the management of sialorrhoea: a systematic review. *Clin Otolaryngol.* 2006;31(4):267-272. doi:10.1111/j.1749-4486.2006.01263.x.
3. Kocdor P, Siegel ER, Tulunay-Ugur OE. Cricopharyngeal dysfunction: a systematic review comparing outcomes of dilatation, botulinum toxin injection, and myotomy. *Laryngoscope.* 2016;126(1):135-141. doi:10.1002/lary.25447.
4. Crowner BE, Torres-Russotto D, Carter AR, Racette BA. Systemic weakness after therapeutic injections of botulinum toxin A: a case series and review of the literature. *Clin Neuropharmacol.* 2010;33(5):243-247. doi:10.1097/WNF.0b013e3181f5329e.
5. Young DL, Halstead LA. Pyridostigmine for reversal of severe sequelae from botulinum toxin injection. *J Voice.* 2014;28(6):830-834. doi:10.1016/j.jvoice.2014.04.010.
6. Boerner RM, Young DL, Gnagi SH, White DR, Halstead LA. Pyridostigmine for the reversal of severe adverse reactions to botulinum toxin in children. *J Pediatr.* 2018;194:241-243. doi:10.1016/j.jpeds.2017.11.013.