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Effectiveness of Botulinum Toxin (Botox) for Treatment of Nystagmus: A review

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ABSTRACT

Nystagmus is an eye movement disorder affecting both children and adults and exists in two main types; congenital and acquired. Botulinum toxin (Botox) is a neurotoxin protein produced by the Clostridium botulinum bacterium. It prohibits the production of the acetylcholine neurotransmitter from endings of axons at the neuromuscular junction, therefore inducing flaccid paralysis. Botulinum toxin has been utilized as a therapeutic agent in both congenital and acquired nystagmus. This review aims to assess the efficacy of botulinum toxin in the treatment of nystagmus compared with other alternative conservative or surgical options. Since most of the research and reviews are on the use of Botox in many types of strabismus, but very little has touched on the results and uses of Botox in cases of nystagmus, it was very interesting to review the research more about this topic. As the treatment of nystagmus cases with surgery is still considered one of the most difficult decisions for strabismus doctors Botox helps a lot.

Keywords: *Botulinum toxin, Nystagmus, Effectiveness, Treatment*

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INTRODUCTION

Nystagmus is an eye movement disorder characterized by rapid, uncontrollable repetitive eye movements. These movements may be up and down, side to side, or in a circular pattern. It may be congenital or acquired, continuous or paroxysmal with head positioning triggers (Dell'Osso *et al*., 1979).

Nystagmus affects both children and adults and exists in two main types; congenital and acquired (Gottlob, 2000). Its prevalence in the general population was 24/10,000 population (Sarvananthan *et al*., 2009).

Botulinum toxin (Botox) is a neurotoxic exotoxin protein produced by the Clostridium botulinum bacterium (anaerobic, gram-positive) and related species (Montecucco & Molgó, 2005). It prohibits the production of the acetylcholine neurotransmitter from endings of axons at the neuromuscular junction, therefore inducing flaccid paralysis (Figgitt & Noble, 2002). It causes botulism disease (Shukla & Sharma, 2005). However, it is also utilized for medical and cosmetic purposes (Al-Ghamdi *et al*., 2015; Janes *et al*., 2021).

There are known main 7 types of botulinum toxin (A, B, C1, C2, D, E, F, and G) (Rosales *et al*., 2006; Janes *et al*., 2021). Types A and B are responsible for inducing human diseases as well and they are used for medical and cosmetic purposes commercially and medically (Blumetti *et al*., 2019; Farag *et al*., 2020).

Botulinum toxin A has been utilized as a therapeutic agent in both congenital and acquired nystagmus and it has been shown that it is effective in treating eye movement disorders beyond 1-3 months (Leigh *et al*., 1992; Ruben *et al*., 1994; Averbuch-Heller, 1999; Dutton & Fowler, 2007; Wan *et al*., 2021).

Botulinum toxin has also a therapeutic effect in helping the improvement of visual acuity by relieving the perception of moving images (oscillopsia) in cases of acquired nystagmus (Witmanowski & Błochowiak, 2020).

The purpose of this review was to investigate the advantages and adverse effects of botulinum toxin as a therapeutic intervention for nystagmus.

RESULTS AND DISCUSSION

Mechanism of action

Botulinum neurotoxin specifically binds the presynaptic recognition sites of neurons` ends of the cholinergic nerve terminals and reduces the release of acetylcholine (Li *et al*., 2010), causing neuromuscular effect and thus flaccid paralysis (Montecucco & Molgó, 2005; Li *et al*., 2010; Cissé *et al.,* 2024). Then, proximal axonal sprouts lead to the formation of a new neuromuscular junction, thus, inducing muscle reinnervation and overall recovery (de Paiva *et al*., 1999).

Injection of botulinum toxin (Botox) into extraocular muscles causes a transient paralysis of these muscles and its long-term impact on ocular alignment can be explained by two mechanisms; the disturbance of a balanced system of agonist-antagonist extraocular muscles and the regaining the effect of binocular visual system in central control of alignment (Wan *et al*., 2021).

The injection of Botulinum toxin in large amounts or at high doses enlarges the diffusion area, thus increasing the potential complications of the drug (Walker & Dayan, 2014).

Botulinum toxin starts to produce an effect within 24-72 hours after injection and reaches its maximum effect within 1-2 weeks days (De Almeida *et al*., 2011).

Effectiveness of Botulinum toxin in the treatment of nystagmus

Injecting botulinum toxin directly into the extraocular muscle has been demonstrated to be an effective treatment for various forms of nystagmus (Leigh *et al*., 1992; Ruben *et al*., 1994; Carruthers, 1995; Lennerstrand *et al*., 1998; Dutton & Fowler, 2007; Thurtell & Leigh, 2012). Nevertheless, employing the retrobulbar route for administering botulinum toxin offers several benefits compared to directly injecting it into the extraocular muscles (specifically the medial and lateral rectus muscles). These advantages include reduced muscular damage, simpler execution, lower cost, the ability to affect multiple muscles with a single injection, and the absence of a need for electromyography (Repka *et al*., 1994). However, the retrobulbar route of administering botulinum toxin has a significant drawback. It requires multiple injections around the eye, which physicians and patients often find unacceptable. Additionally, there is a risk of diplopia and ptosis occurring due to the toxin spreading to nearby tissues (Leigh *et al*., 1992; Tomsak *et al*., 1996; Averbuch-Heller, 1999; Crouch, 2006; Dutton & Fowler, 2007).

A review of the literature yielded only some case reports and case series evaluated the effectiveness of Botulinum toxin in treating nystagmus. Venturi *et al*. (2021) documented the efficacy of injecting botulinum toxin into the four horizontal rectus muscles as a treatment for an adult female patient with acquired Periodic Alternating Nystagmus (PAN) and oscillopsia. After administering baclofen, gabapentin, and surgery, they noted that Snellen's Visual Acuity improved to 6/12 in both eyes, accompanied by oscillopsia. After receiving botulinum toxin treatment, the visual acuity (VA) improved to 6/5 and 6/6 on the right and left eye, respectively. There were noticeable improvements in both the subjective and objective measures of nystagmus and oscillopsia. The researchers determined that botulinum toxin can be employed as a viable treatment modality for acquired PAN, especially in instances where patients are unable to tolerate or do not respond to conventional medical interventions. However, it is not recommended as a long-term therapeutic option (Venturi *et al*., 2021). Chen *et al*. (2016) reported an old female patient of nystagmus in brainstem cavernous malformation treated with bilateral retrobulbar injections of botulinum toxin A. They observed an immediate reduction in nystagmus and oscillopsia and improvements in visual acuities. However, after 1-3 months of injection, they observed a substantial reduction in nystagmus amplitudes at multiple dimensions (39-100%) using three-dimensional infrared oculography. This improvement decreased in both eyes within 6 months to one year. They concluded that botulinum toxin is a safe and effective drug in symptomatic nystagmus after failure of medical treatment (Chen *et al*., 2016).

Ruben *et al*. (1994) evaluated the impact of botulinum toxin A injections (either directly into the horizontal recti muscle or retrobulbar); given at 3-4 months intervals on the visual acuity of 12 patients with acquired nystagmus and oscillopsia. They observed improvements in visual acuity in some patients and not all (8 out of 12). However, transient ptosis was the main complication (Ruben *et al*., 1994). Also, Leigh *et al*. (1992) documented the administration of botulinum toxin into the horizontal rectus muscles of the right eyes of two patients with acquired nystagmus. They noted that the administration of botulinum toxin effectively eliminated the side-to-side movement of the involuntary eye movement (nystagmus) in the two patients for almost 2 months, and this was accompanied by a noticeable improvement in their vision. Nevertheless, the vertical and torsional aspects of the nystagmus were unaffected in both patients. Nevertheless, they determined that the efficacy of botulinum toxin in treating acquired nystagmus may be restricted due to its associated side effects, such as diplopia and ptosis (Leigh *et al*., 1992; Pavlova, 2023).

It has been reported that it is difficult to be used in children due to two main reasons; first, the need for strong sedation, and second, the higher possibility of leakage of the toxin into the levator palpebral superioris muscle leading to ptosis (Rowe *et al*., 2005).

Side effects

Transient mild side effects

These include reversible, self-limited as well as localized side effects. They exist within a few days post-injection and often disappear without any intervention (Witmanowski & Błochowiak, 2020). Among these side effects are (1) bruising/ecchymosis at the site of injection which affects between 11% and 15% of patients and is produced due to injury of blood vessels at the injection site; mainly around the ocular area and can be prevented/reduced by applying pressure and ice packs at the site of injection (Vartanian & Dayan, 2005; Suchy, 2024). (2) hematoma, which is due to more severe injury of blood vessels can develop soon following the injection and can stay for a long time after injection and can progress to the abscess. Managing this by simple tamponade at the time of hemorrhage and possible antibiotics could prevent the formation of a hematoma/abscess or at least decrease its size in addition, patients should stop the use of anticoagulants two weeks before the injection. Also, the treated area should not be massaged for up to two hours after injection to prohibit the absorption of the injected toxin and decrease its spread to surrounding areas (Klein, 2001). local pain induced by needle puncturing of the skin; particularly if inappropriate needle size was used (Ward *et al*., 2012). (4) dry skin and subsequent flakiness as a result of the reduction in the activity of the sweat gland (Vartanian & Dayan, 2005; Diakité *et al.,* 2024). (5) skin infection at the site of injection due to penetration of the skin barrier; if the area was not properly prepared or if the injection was touched by the patient within 6 hours of injection (Kroumpouzos *et al*., 2021). (6) psoriasiform eruption as a result of disturbances between botulinum toxin and nerve fibers (Ward *et al*., 2012). (7) headache since the botulinum toxin initially causes muscle spasms, before complete paralysis or due to the needle hitting the periosteum also stress of injection can have a role in this regard headache is always transient, however, in rare cases, it may last for weeks (Vartanian & Dayan, 2005; Small, 2014). (8) Paresthesia or dysesthesia which is a rare side effect that may occur as a result of nerve trauma (Small, 2014). (9) Hypoesthesia due to the localized antinociceptive characteristics of botulinum toxin (Vartanian & Dayan, 2005). (10) dry mouth and flu-like

malaise which are usually mild (Vartanian & Dayan, 2005). (11) allergic reactions ranging from redness and edema localized to the injection site to diffuse erythema, generalized urticaria, and even anaphylactic shock in rare cases (Small, 2014).

Serious side effects

These complications can arise from the incorrect injection of botulinum toxin into the wrong muscle group or its subsequent spread from the injection site to nearby muscles. This can result in temporary paralysis of the affected muscles, as the toxin is capable of spreading up to a distance of 30-45 mm (Nigam & Nigam, 2010). Another serious side effect is systemic anaphylactic reactions or botulism-like features, which can occur as a result of the systemic spread of toxin (Coté *et al*., 2005; Paget *et al*., 2018). Dysphagia and muscle weakness; where the US Food and Drug Administration (FDA) reported 36 cases with dysphagia and muscle weakness as a result of botulinum toxin injection (Rowe *et al*., 2005). In rare cases, also arrhythmia, heart attack, respiratory arrest seizures, and even death may occur (Coté *et al*., 2005).

Despite those side effects, botulinum toxin is generally regarded as a safe medication in clinical settings (Nigam & Nigam, 2010).

Contraindications

Botulinum toxin shouldn't be given to women who are pregnant or breastfeeding, to people who are known to be allergic to any part of the preparation, or to people who have neuromuscular disease or coagulopathies (Klein, 2001; Rohrich *et al*., 2003).

CONCLUSION

Botulinum toxin has been successfully used for over two decades to treat nystagmus by injecting it directly into the extraocular muscle. It has not been widely used. Further investigation into the barriers to using botulinum toxin in trying nystagmus extensively is highly recommended.

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REFERENCES

Al-Ghamdi, A. S., Alghanemy, N., Joharji, H., Al-Qahtani, D., & Alghamdi, H. (2015). Botulinum toxin: Non cosmetic and off-label dermatological uses. *Journal of Dermatology & Dermatologic Surgery*, *19*(1), 1-8. doi:10.1016/j.jdds.2014.06.002

Averbuch-Heller, L. (1999). Acquired nystagmus. *Current Treatment Options in Neurology*, *1*(1), 68-73. doi:10.1007/s11940-999-0034-4

Blumetti, F. C., Belloti, J. C., Tamaoki, M. J., & Pinto, J. A. (2019). Botulinum toxin type A in the treatment of lower limb spasticity in children with cerebral palsy. *Cochrane Database of Systematic Reviews*, (10), CD001408. doi:10.1002/14651858.CD001408.pub2

Carruthers, J. (1995). The treatment of congenital nystagmus with Botox. *Journal of Pediatric Ophthalmology & Strabismus*, *32*(5), 306-308.

Chen, Y. R., Fredrick, D., Steinberg, G. K., & Liao, Y. J. (2016). Treatment of nystagmus in brainstem cavernous malformation with botulinum toxin. *Cureus*, *8*(4), e553. doi:10.7759/cureus.553

Cissé, C., Konaré, M. A., Samaké, M., & Togola, I. (2024). Anti-inflammatory Activity of Two Antitussive Plants for Children: Sericanthechevalieri and Ceibapentandra. *International Journal of Pharmaceutical Research and Allied Sciences, 13*(4), 19-28.

Coté, T. R., Mohan, A. K., Polder, J. A., Walton, M. K., & Braun, M. M. (2005). Botulinum toxin type A injections: Adverse events reported to the US food and drug administration in therapeutic and cosmetic cases. *Journal of the American Academy of Dermatology*, *53*(3), 407-415. doi:10.1016/j.jaad.2005.06.011

Crouch, E. R. (2006). Use of botulinum toxin in strabismus. *Current Opinion in Ophthalmology*, *17*(5), 435-440. doi:10.1097/01.icu.0000243018.97627.4c

De Almeida, A. R. T., Secco, L. C., & Carruthers, A. (2011). Handling botulinum toxins: An updated literature review. *Dermatologic Surgery*, *37*(11), 1553-1565. doi:10.1111/j.1524-4725.2011. 02087.x

Dell'Osso, L. F., Schmidt, D., & Daroff, R. B. (1979). Latent, manifest latent, and congenital nystagmus. *Archives of Ophthalmology*, *97*(10), 1877-1885.

dePaiva, A., Meunier, F. A., Molgó, J., Aoki, K. R., & Dolly, J. O. (1999). Functional repair of motor endplates after botulinum neurotoxin type a poisoning: Biphasic switch of synaptic activity between nerve sprouts and their parent terminals. *Proceedings of the National Academy of Sciences*, *96*(6), 3200-3205.

Diakité, A. S., Ambeu-Loko, C. N. M., Yapi, A. D., Logé, C., Kacou, A., Kra, S., Baratte, B., Bach, S., Ruchaud, S., Sissouma, D., et al. (2024). Design and synthesis of functionalized 2,4-diamino-1,3,5-triazines, potential inhibitors involved in immune and inflammatory response. *International Journal of Pharmaceutical Research and Allied Sciences, 13*(4), 1-11.

Dutton, J. J., & Fowler, A. M. (2007). Botulinum toxin in ophthalmology. *Survey of Ophthalmology*, *52*(1), 13-31. doi:10.1016/j.survophthal.2006.10.003

Farag, S. M., Mohammed, M. O., El-Sobky, T. A., ElKadery, N. A., & ElZohiery, A. K. (2020). Botulinum toxin A injection in treatment of upper limb spasticity in children with cerebral palsy: A systematic review of randomized controlled trials. *JBJS Reviews*, *8*(3), e0119. doi:10.2106/JBJS.RVW.19.00119

Figgitt, D. P., & Noble, S. (2002). Botulinum toxin B: A review of its therapeutic potential in the management of cervical dystonia. *Drugs*, *62*(4), 705-722. doi:10.2165/00003495-200262040-00011

Gottlob, I. (2000). Nystagmus. *Current Opinion in Ophthalmology*, *11*(5), 330-335.

Janes, L. E., Connor, L. M., Moradi, A., & Alghoul, M. (2021). Current use of cosmetic toxins to improve facial

aesthetics. *Plastic and Reconstructive Surgery*, *147*(4), 644e-657e. doi:10.1097/PRS.0000000000007762

Klein, A. W. (2001). Complications and adverse reactions with the use of botulinum toxin. *Seminars in Cutaneous Medicine and Surgery, 20*(2), 109-120. doi:10.1053/sder.2001.25964

Kroumpouzos, G., Kassir, M., Gupta, M., Patil, A., & Goldust, M. (2021). Complications of botulinum toxin A: An update review. *Journal of Cosmetic Dermatology*, *20*(6), 1585-1590. doi:10.1111/jocd.14160

Leigh, R. J., Tomsak, R. L., Grant, M. P., Remler, B. F., Yaniglos, S. S., Lystad, L., & Dell'Osso, L. F. (1992). Effectiveness of botulinum toxin administered to abolish acquired nystagmus. *Annals of Neurology*, *32*(5), 633-642. doi:10.1002/ana.410320506

Lennerstrand, G., Nordbø, O. A., Tian, S., Eriksson-Derouet, B., & Ali, T. (1998). Treatment of strabismus and nystagmus with botulinum toxin type A. An evaluation of effects and complications. *Acta Ophthalmologica Scandinavica*, *76*(1), 27-37.

Li, B., Peet, N. P., Butler, M. M., Burnett, J. C., Moir, D. T., & Bowlin, T. L. (2010). Small molecule inhibitors as countermeasures for botulinum neurotoxin intoxication. *Molecules*, *16*(1), 202-220. doi:10.3390/molecules16010202

Montecucco, C., & Molgó, J. (2005). Botulinal neurotoxins: Revival of an old killer. *Current Opinion in Pharmacology*, *5*(3), 274-279. doi:10.1016/j.coph.2004. 12.006

Nigam, P. K., & Nigam, A. (2010). Botulinum toxin. *Indian Journal of Dermatology*, *55*(1), 8-14. doi:10.4103/0019-5154.60343

Paget, S. P., Swinney, C. M., Burton, K. L., Bau, K., & O'Flaherty, S. J. (2018). Systemic adverse events after botulinum neurotoxin A injections in children with cerebral palsy. *Developmental Medicine & Child Neurology*, *60*(11), 1172-1177. doi:10.1111/dmcn.13995

Pavlova, Z. (2023). Properties of 3D-printed complete dentures – clarified and unclarified aspects. *Annals of Dental Specialty, 11*(4), 77-86.

Repka, M. X., Savino, P. J., & Reinecke, R. D. (1994). Treatment of acquired nystagmus with botulinum neurotoxin A. *Archives of Ophthalmology*, *112*(10), 1320-1324. doi:10.1001/archopht.1994.01090220070025

Rohrich, R. J., Janis, J. E., Fagien, S., & Stuzin, J. M. (2003). The cosmetic use of botulinum toxin. *Plastic and Reconstructive Surgery*, *112*(5), 177S-188S. doi:10.1097/01.PRS. 0000082208.37239.5B

Rosales, R. L., Bigalke, H., & Dressler, D. (2006). Pharmacology of botulinum toxin: Differences between type Apreparations. *European Journal of Neurology*, *13*, 2-10. doi:10.1111/j.1468-1331.2006.01438.x

Rowe, F. J., Noonan, C. P., & Nayak, H. (2005). Botulinum toxin as a treatment option for decompensating intermittent strabismus in children. *Transactions of the 30th European Strabismological Association*, 8-11.

Ruben, S. T., Lee, J. P., O'Neil, D., Dunlop, I., & Elston, J. S. (1994). The use of botulinum toxin for treatment of acquired nystagmus and oscillopsia. *Ophthalmology*, *101*(4), 783-787. doi:10.1016/S0161-6420(94)31265-6

Sarvananthan, N., Surendran, M., Roberts, E.O., Jain, S., Thomas, S., Shah, N., Proudlock, F. A., Thompson, J. R., McLean, R. J., Degg, C., et al. (2009). The prevalence of nystagmus: The Leicestershire nystagmus survey. *Investigative Ophthalmology & Visual Science*, *50*(11), 5201-5206. doi:10.1167/iovs.09-3486

Shukla, H. D., & Sharma, S. K. (2005). Clostridium botulinum: A bug with beauty and weapon. *Critical Reviews in Microbiology*, *31*(1), 11-18. doi:10.1080/10408410590912952

Small, R. (2014). Botulinum toxin injection for facial wrinkles. *American Family Physician*, *90*(3), 168-175.

Suchy, W. (2024). Beyond the barrier: The endothelium's unsung role in physiology & pathology. *International Journal of Pharmaceutical Research and Allied Sciences, 13*(4), 12-18.

Thurtell, M. J., & Leigh, R. J. (2012). Treatment of nystagmus. *Current Treatment Options in Neurology*, *14*, 60-72. doi:10.1007/s11940-011-0154-5

Tomsak, R. L., Remler, B. F., Averbuch-Heller, L., Chandran, M., & Leigh, R. J. (1996). Unsatisfactory treatment of acquired nystagmus with retrobulbar injection of botulinum toxin. *Journal of Neuro-Ophthalmology, 16*, 62. doi:10.1097/00041327-199603000-00057

Vartanian, A. J., & Dayan, S. H. (2005). Complications of botulinum toxin A use in facial rejuvenation. *Facial Plastic Surgery Clinics of North America*, *13*(1), 1-10. doi:10.1016/j.fsc.2004.04.008

Venturi, N., Adams, G., & Theodorou, M. (2021). The use of botulinum toxin in a case of acquired periodic alternating nystagmus. *The British and Irish Orthoptic Journal*, *17*(1), 85. doi:10.22599/bioj.170

Walker, T. J., & Dayan, S. H. (2014). Comparison and overview of currently available neurotoxins. *The Journal of Clinical and Aesthetic Dermatology*, *7*(2), 31-39.

Wan, M. J., AlShaker, S., & Hunter, D. G. (2021). Use of botulinum toxin in ophthalmology. *Botulinum Toxin Therapy*, 147-160. doi:10.1007/164_2019_325

Ward, N. L., Kavlick, K. D., Diaconu, D., Dawes, S. M., Michaels, K. A., & Gilbert, E. (2012). Botulinum neurotoxin A decreases infiltrating cutaneous lymphocytes and improves acanthosis in the KC-Tie2 mouse model. *The Journal of Investigative Dermatology*, *132*(7), 1927-1930. doi:10.1038/jid.2012.60

Witmanowski, H., & Błochowiak, K. (2020). The whole truth about botulinum toxin–A review. *Advances in Dermatology and Allergology*, *37*(6), 853-861. doi:10.5114/ada.2019.82795