MERIT RESEARCH JOURNALS
www.meritresearchjournals.org

Merit Research Journal of Medicine and Medical Sciences (ISSN: 2354-323X) Vol. 6(2) pp. 068-072, February, 2018
Available online http://www.meritresearchjournals.org/mms/index.htm


*Original Research Article*

# Systematic Evaluation of Adverse Reactions That May Occur After Injection of Type-A Botulinum Toxin in Patients with Spasmodic Torticollis Admitted to Emergency Department

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**Abstract**

**Type-A botulinum toxin (BTX-A) is today frequently used for cosmeceutical purposes. In addition, it is used extensively in the treatment of the patients with spasmodic torticollis in neurosurgery practice. However, patients admitted to the emergency department with adverse reactions / adverse events observed, especially after these applications constitute a severe problem. In this study, it was aimed to systematically evaluate the adverse reactions or events reported in the literature after administering BTX-A injections to the patients with spasmodic torticollis between Nov-1-1997 and Feb-13-2018. The data obtained from this research, it will be able to be seen a bigger image about these negativities that may arise. Thus, the management strategies for the treatment of such cases admitted to emergency departments can be planned more easily.**

**Keywords:** Adverse reactions, Adverse events, Spasmodic torticollis, Type-A botulinum toxin injections

## INTRODUCTION

Type-A botulinum toxin (BTX-A) is clinically used for following medical purposes: a) in the treatment of the anterocollis, a subtype of cervical dystonia, or in the treatment of the antherocaput associated with other types of focal dystonia (Finsterer et al., 2014); b) in the treatment of the involuntary contraction of the cervical spine muscles (Finiels et al., 2014); c) using preoperatively to prevent instrument failure in the patients with athetoid cerebral palsy (Kim et al., 2014); d) in the treatment of the cervical spondyloticmyelopathy (Pancucci et al., 2011) e) in the treatment of the painful and moving joints in addition to epidural spinal cord stimulation (Miakawa et al., 2010) and finally in the treatment of the low back pain (Chou et al., 2009). In conventional radiofrequency neurotomy, BTX-Ais administered by performing periarticular injections (Lee et al., 2010; Simopoulos et al., 2015) and the injections are performed on the piriformis muscle in sciatic perineural oedema treated with BTX-A (Wu et al., 2015).

In addition, researches have been reported in the literature concerning the effects of botulinum to-xins on nociceptive neurons in the live mammals (in vivo)

**Table 1.** The frequency of the studies by years.

| Keywords | Total | Clinical trial | Review | Date range |
|---|---|---|---|---|
| Emergency Department | 212.828 | 9.055 | 21.086 | 2018 Feb 13 – 1922 Oct |
| Emergency Medicine | 125.062 | 5.680 | 15.218 | 2018 Feb 13 – 1934 Feb 28 |
| Neurosurgery | 322.427 | 12.249 | 32.383 | 2018 Feb 13 – 1927 Mar |
| Adverse reaction | 71.149 | 6.656 | 7.742 | 2018 Feb 8 – 1933 Mar 20 |
| Adverse events | 165.707 | 47.890 | 31.573 | 2018 Feb 13 – 1949-Jul |
| *Type-A Botulinum Toxin* | 9.066 | 1.398 | 1.454 | 2018 Feb 7 – 1946 May 17 |
| Torticollis | 4.396 | 195 | 402 | 2018 Feb – 1884 Jun 14 |
| Adverse reaction/Adverse events + *Type-A Botulinum Toxin* + Torticollis | 5 | 1 | 0 | 1997 Nov - 2005 Jan |

(Xiao et al., 2011).

The main features of the cervical dystonia are abnormal head and neck postures caused by involuntary contractions of muscles. Along with abnormal head posture, repetitive or jerk-like movements accompanied by postural tremor and aches may be present. Cervical dystonia is also called spasmodic torticollis (ST). ST is mainly characterized by the presence of the jerk in the head and spasms in the neck. However, the same symptoms have not been observed in 30% of the cervical dystonia cases (Matthews et al., 1978).

In addition, BTX-A injections are carried out in a variety of areas and it is believed that these injections are safe. However, many adverse reactions have been reported, including dysphagia, general paralysis, respiratory depression, and death due to the focal injection of toxin (Fan et al., 2016).

This study was conducted with the aim of systematic evaluation of the reported adverse reactions of botulinum toxin, which shows its effect by blocking the chemical stimuli in the stimulus nerve cells located in the area where it is administered after injection to prevent muscle contraction, in the patients with ST admitted to the emergency department.

## MATERIALS AND METHODS

### Search Strategy

Clinical trials, conducted between Nov-1-1997 and Feb-13-2018, in the Cochrane Collaboration, the Cochrane Library, Ovid MEDLINE, ProQuest, the National Library of Medicine, and the PubMed electronic databases, were scanned using terms "OR", "AND" without language and country restrictions. Keywords involving “Emergency Department”, “Emergency Medicine”, “Neurosurgery”, “*Type-A Botulinum Toxin*”, “torticollis”, “adverse reaction”, “adverse events” were used individually or in combinations of words (Table 1).

Of all the studies, those with high evidence were selected. The study carried out by Lijmer et al (1999) was used to determine the level of evidence of the studies. Subsequently, the data obtained were checked considering the Transparent Reporting of the Systematic Review (PRISMA) (2015). Comments, letters, editorials, protocols, guides, meta-analyzes and compilations were also excluded from the study (Ali et al., 2016; Gumustas et al., 2017; Karaarslan et al., 2017; Topuk et al., 2017; Yilmaz et al., 2016;)

### Accumulation and Evaluation of Data

The authors independently selected the included studies. The risk of selection bias, which might be caused by potentially masking, has also been investigated. All studies were examined by four authors *(FSA, IY, TC, NK)* to ensure accuracy. Among these authors, FSA and IY argued that BTX-A injections should be evaluated not only in the "torticollis" but also in all cervical dystonia. Regarding this disagreement, the neurosurgeons TC and NK stated that cervical dystonia might also be referred to as ST, but this use was not correct. This disagreement was eliminated, proving that ST was mainly characterized by the presence of the jerk in the head and spasms in the neck in the light of the studies carried out before in the literature (Matthews et al., 1978). In the event of the occurrence of the similar disagreements among the authors, consensus was reached on the issue by re-consulting all authors in the presence of experienced authors (*HO and OA*).

### Statistical Analyzes

Initially, the use of the Review Manager Software Program in Windows XP was planned to evaluate the data obtained from appropriate studies. In this way, the heterogeneity was measured by the Cochrane Q test. However, descriptive statistical evaluations were performed using the Microsoft Excel program (2013 version) since common data could not be found after the screening process.

**Table 2.** Distribution of studies by years after full text review.

| Author(s) | Date |
|---|---|
| Li et al.[20] | 2005 |
| Bihari K.[21] | 2005 |
| Brashear et al.[22] | 2000 |
| Wan et al.[23] | 1998 |
| LeWitt and Trosch[24] | 1997 |

## RESULTS

After the initial screening, 324 out of 473 articles in total were examined thoroughly. Only five studies of the highest level of evidence (2005; Bihari, 2005; Brashear et al., 2000; LeeWitt et al., 1997; Li et al., 2005; Wan et al., 1998), in which adverse effects of BTX-A injections, which were administered to the patients with ST, were reported, were assessed (Table 2).

## DISCUSSION

This specific exotoxin, produced by clostridium botulinum, a gram-positive anaerobic bacterium, exhibits its chemical transient paralytic effects by blocking the release of acetylcholine at the neuromuscular junction. Botulinum toxin, which shows its effect by causing temporary paralysis in the muscle activity, is mostly used for cosmeceutical purposes. It may also be used in other medical conditions such as sweating treatment, urinary incontinence due to overactive bladder, migraine treatment, cervical dystonia and ST.

However, many adverse reactions have been reported, including dysphagia, general paralysis, respiratory depression, and death due to the focal injection of toxin. In addition, experimental studies have shown that administering 0.001 microgram toxin per kg body weight to the subjects is sufficient to give rise to the death of the 50% of live mammalian subjects (Niamtu, 2003). In the light of these findings, it is indisputably a scientific fact that this toxin is quite potent.

This toxin was found to be the cause of botulism, a systemic food poisoning, towards the end of the 19th century. In fact, when the literature is examined, it has been observed that the accurate description of the clinical symptoms of the nutritional botulism was published between 1817 and 1822. Some thoughts on the therapeutic use of this toxin, called sausage poisoning, emerged in 1820. In 1822, clinical evaluations of 155 cases of botulism, post mortem studies, animal studies and experiments that the researchers performed bravely in their own body were carried out (Moore et al., 2003).

Botulinum toxin shows its effect by inhibiting peripheral motor conduction, sympathetic and parasympathetic nerve signal transmission without affecting peripheral sensory conduction. In accordance with our modern medicine knowledge, BTX-A has been purified for the first time in the 1920s, and all its muscular and autonomic symptoms have been defined at the same period (Moore et al., 2003).

There are seven serotypes of botulinum toxin. These serotypes have the same pharmacological effect. The toxins block acetylcholine release in the cholinergic autonomic nerves and the neuromuscular junction by binding to the peripheral cholinergic terminals. As a result, this causes the flaccid paralysis and autonomic symptoms. This inhibition consists of the following steps: a) fast, specific and irreversible binding to receptors on the presynaptic nerve surface b) ingested into cell via vesicles c) translocation d) proteolytic toxin activity which blocks acetylcholine release (Moore et al., 2003).

Cervical dystonia is the most common focal dystonia causing abnormal movements and awkward postures of the head. This focal dystonia may cause deterioration in the head posture (torticollis), head tilts to one side (laterocollis), neck flexion (anterocollis) and extension (retrocollis) cervical dystonia is usually an idiopathic dystonia. However, it may also be secondary to other disorders such as trauma, neurological diseases, posterior fossa and cervical cord pathologies. Secondary dystonias are rarely seen and botulinum toxin injections are the most effective form of treatment for idiopathic cervical dystonias (Barr et al., 2017; Charles et al., 2014; Misra et al., 2012).

In this systematic review, it is aimed to examine what may be the adverse reactions observed in the patients admitted to the emergency department following BTX-A injections for the treatment of the ST (Gartlan et al., 1993) which is a focal dystonia.

In the literature, the reported LD50 in human for botulinum toxin with systemic injections is 30-40 Mu/kg. The dose applied to the patients with the cervical dystonia is reported to be 100-200 Mu or 400 Mu (Moore et al., 2003). A Botox vial contains 100 units BTX-A-hemagglutinin complex in sterile lyophilized form, 0.5 mg human albumin and 0.9 mg sodium chloride. In this form, it can be kept frozen for up to four years, in the refrigerator for months and at room temperature for weeks. Statistically, no reduction is observed in toxin potency after six hours at minus 6 °C, but it is reported reduction in toxin potency after 12 hours at minus 6 °C (Gartlan et al., 1993).

It has been indicated in the literature that BTX-A is

generally used by diluting with normal (0.9%) saline, then it is recommended to be administered within four to six hours after reconstitution and finally the remaining amount should be destroyed. It can also be reconstituted with sterile water, but it has been reported that the applications performed in this way cause pain at the injection site (van Laborde et al., 2003). It has been reported that if toxin is scattered around during the application process, it can be inactivated with 0.5% sodium hypochlorite (Moore et al., 2003).

Another crucial point that should not be forgotten is that in the BTX-A applications, the selection of the patient, the appropriate dose, and the injections at appropriate intervals to the appropriate muscles are important criteria for both patient benefit and long-term treatment. The injection is applied directly to the contracting muscles, and so the practitioner should be very familiar with the anatomy of the neck muscles and the adjacent sites.

Li and colleagues (2005) reported in their research the death of the female patient with ST and seventh cranial nerve impairment who treated with the BTX-A, approved by the Food and Drug Administration, -lidocaine mixture. It was reported that the cause of death was anaphylaxis caused by this Botox-lidocaine mixture. Although the anaphylaxis could not be definitively proven to be due to Botox alone, this was the first case where an adverse reaction related to Botox was reported (Li et al., 2005).

Bihari (2005) evaluated in a study the effectiveness of two different BTX-A preparations in the treatment of the 48 patients, 12 of whom diagnosed with cervical dystonia. Of the 48 patients, 19 experienced at least one adverse drug reaction during treatment. The most common adverse reactions were reported to be hemifacial spasm and neck weakness for cervical dystonia (Bihari, 2005).

Brashear et al. (2000) indicated that although botulinum toxin was widely used in patients with idiopathic cervical dystonia, there was no evidence about when and why these patients stopped treatment with BTX-A. In this study, conducted with 155 patients, they suggested that the causes of stopping of BTX-A treatment were adverse events and changes in dose and / or frequency (Brashear et al, 2000).

Wan et al. (1998) applied two kinds of BTX-A preparations to 113 patients with cervical dystonia. In this research, they reported the appearance of the adverse events such as skin rash in some patients (n=4) within a few days after the injections.

LeWitt and Trosch (1997) underlined in a study that idiosyncratic adverse responses such as bilateral ptosis might be appeared after the repeated dose injections of BTX-A on the cervical region muscles.

After evaluating the data obtained from our literature review, only five studies containing all our search criteria were found. This can be considered as a weakness of this study. In our systematic review, increasing the number of studies, which were examined, was possible by extending our search criteria. However, we think that this situation may give rise to further confusion among the results and it may prevent making binding inferences. The evidences that allow making definitive conclusions about the adverse reactions occurring after BTX-A injections in the patients with ST are unfortunately inadequate in the literature. Making definitive conclusions may only be possible with large-scale, multicenter and multidisciplinary clinical trials.

## CONCLUSIONS

Early application of antitoxin in patients with a detrimental or unintended effect resulting from the use of a biological, pharmaceutical or pharmacological product in normal doses for the prevention, diagnosis or treatment of a disease or for the alteration, correction or amelioration of a physiological function should be the mainstay in the management of emergency medicine physicians. The time window needs to be well defined to determine the clinical effectiveness of such pharmaceuticals. Given the side effects / adverse reactions of the drug to the patients and the financial burden to the health economies, the selection of the patient, the correct indications and the importance of the application will be better understood. For this reason, it is important to raise awareness on this issue amongst the emergency physicians or neurosurgeons in hospitals under the guidance of medical pharmacologists.

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