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Botulinum toxin in the treatment of sialorrhea

Botulinski toksin u lečenju sijaloreje

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Abstract

Background/Aim. Botulinum toxin-A (BTX-A) is known to block the release of acetylcholine from motor and autonomic nerve terminals and may significantly decrease saliva production when injected intraglandulary. The aim of this study was to evaluate effects of BTX-A injections in the treatment of disabling sialorrhea in various neurological disorders. **Methods.** This study included 19 consecutive patients with significant sialorrhea associated with various neurological disorders. Out of them 13 patients were with Parkinson's disease, two with pantothenate kinase-associated neurodegeneration, two with multiple system atrophy, one with Wilson's disease, and one patient with postoperative sialorrhea. Botulinum toxin-A (Dysport®, Ipsen Pharma) was injected into the parotid glands with (n = 7 patients) or without (n = 12 patients) ultrasound guidance. All the patients were scored before and after the treatment and in weekly intervals thereafter using the salivation item of the part II (Activities of Daily Living) of the Unified Parkinson's Disease Rating Scale (UPDRS). **Results.** Thirteen patients (68%) reported beneficial effect of BTX-A injection, while 6 of them (32%) had no response at all. The sialorrhea scores before and after the treatment were 3.1 ± 0.1 (range 2–4) and 1.8 ± 0.1 (range 0–3), respectively ($t = 5.636$; $p < 0.001$). There was no difference in the magnitude of response between the groups with ($t = 4.500$; $p = 0.004$) and without ($t = 3.674$; $p = 0.005$) ultrasound control of injection sites. Adverse effects were registered in 5 patients (26%). **Conclusions.** Botulinum toxin-A injections to easily accessible parotid glands, without necessity for ultrasound guidance, are safe and efficaceous treatment for sialorrhea in different neurological disorders.

Key words:
sialorrhea; parkinson disease; neurodegenerative diseases; botulinum toxins.

Apstrakt

Uvod/Cilj. Botulinski toksin A (BTX-A) blokira oslobađanje acetilholina iz motornih i autonomnih nervnih završetaka, te može znatno da umanji stvaranje pljuvačke kada se ordinira intraglandularno. Cilj ove studije bio je da se utvrde efekti primene BTX-A u lečenju sijaloreje kod raznih neuroloških poremećaja. **Metode.** Ovom studijom bilo je obuhvaćeno 19 konsekutivnih bolesnika sa značajnom sijalorejom izazvanom različitim neurološkim bolestima. Od tog broja 13 bolesnika je bilo sa Parkinsonovom bolesti, dva sa pantotenat kinaza-udruženom neurodegeneracijom, dva sa multiplom sistemskom atrofijom, jedan sa Wilson-ovom bolesti i jedan bolesnik sa postoperativnom sijalorejom. Botulinski toksin A (Dysport®, Ipsen Pharma) injektovan je u parotidne žlezde kod bolesnika sa (n = 7) i bez (n = 12) ultrazvučnog navođenja. Svi bolesnici ocenjivani su pre i posle tretmana u nedeljnim intervalima uz primenu dela UPDRS skale koji se odnosi na hipersalivaciju (*Unified Parkinson's Disease Rating Scale* – UPDRS, *Part II Activity of Daily Living*). **Rezultati.** Ukupno 13 bolesnika (68%) saopštilo je povoljno dejstvo injektovanja BTX-A, dok je šest bolesnika (32%) ostalo bez ikakve reakcije. Ocene stepena sijaloreje pre i posle tretmana bile su 3,1 ± 0,1 (opseg 2–4) i 1,8 ± 0,1 (opseg 0–3), respektivno ($t = 5,636$; $p < 0,001$). Nije bilo razlike u magnitudi reakcije između grupa sa ($t = 4,500$; $p = 0,004$) i bez ($t = 3,674$; $p = 0,005$) ultrazvučnog upravljanja mestima injektovanja. Neželjeni efekti zabeleženi su kod pet bolesnika (26%). **Zaključak.** Injektiranje botulinskog toksina A u lako pristupačne parotidne žlezde, bez potrebe za ultrazvučnim navođenjem, bezbedno je i efikasno u lečenju sijaloreje kod različitih neuroloških bolesti.

Ključne reči:
sijaloreja; parkinsonova bolest; neurodegenerativne bolesti; botulinski toksini.

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Introduction

Sialorrhea, defined as an overflow of saliva from the mouth (drooling), negatively affects both patient's quality of life and social interactions [1, 2]. Its etiology includes acute and chronic neurological disorders (Parkinson's disease, Wilson's disease, motor neuron disease, multiple system atrophy, pantothenate kinase-associated neurodegeneration, bulbar and pseudobulbar palsy, etc.), hypersecretion (inflammatory processes in oral cavity), adverse effects of some drugs, or anatomic abnormalities affecting oral cavity [3].

Mild cases of sialorrhea may be treated pharmacologically (i.e. anticholinergics, although their use is often restricted by side effects), while more severe cases of drooling are eventually referred to surgery [4].

Kerner [5] noted severe dryness of mouth in patients with botulism, and was the first to suggest possibility that botulinum toxin might be used to treat sialorrhea. Botulinum toxin-A (BTX-A) blocks the release of acetylcholine from motor and autonomic nerve terminals, and, when injected intraglandulary, it may significantly decrease saliva production and can be beneficial in excessive sialorrhea [6-8]. However, a number of issues (doses, sites of injections, method of application) is still open.

The aim of this study was to evaluate the effects of BTX-A injections to the parotid glands in the treatment of disabling sialorrhea in various neurological disorders.

Methods

The study comprised 19 consecutive patients with sialorrhea associated with various neurological disorders (Table 1), who were treated with BTX-A injections at the Institute of Neurology, Belgrade from January 2006 to January 2007. All the patients rated their sialorrhea with score ≥ 2 according to the salivation item of the part II (Activities of Daily Living) of the Unified Parkinson's Disease Rating Scale (UPDRS) [9]. None of them had problems with swallowing of solid food. The study was approved by the Ethical Committee of the Clinical Center of Serbia. The patients were included in the study after giving informed and written consent.

Botulinum toxin-A (Dysport®; Ipsen Pharma) was injected (final concentration 10U/0.1ml; 1 ml syringe using a 22-gauge needle penetrating to a depth of 1 cm) into preauricular portion of parotid glands, behind the angle of the ascending mandibular rami, and then into the inferoposterior portion of the parotid gland lying just before the mastoid processes. In order to avoid chewing difficulties, injections were applied after clinical detection of the masseter muscle (palpation). Botulinum toxin-A was applied with and without ultrasound guidance in 7 and 12 patients, respectively. All the patients were scored before and after the treatment, using the UPDRS salivation item and clinically followed in weekly intervals (0 = normal; 1 = slight but definite excess of saliva in mouth, may have night-time drooling; 2 = moderately excessive saliva, may have minimal drooling; 3 = marked excess of saliva with some drooling; 4 = marked drooling, requires constant tissue or handkerchief)

Results

Six patients (32%) did not respond at all, while 13 patients (68%) reported beneficial effect of BTX-A injection (change in drooling score ≥ 1 point). The sialorrhea scores before and after the treatment were 3.1 ± 0.1 (range 2-4) and 1.8 ± 0.1 (range 0-3), respectively ($t = 5.636$; $p < 0.001$). There was no difference in the magnitude of response between the groups with ($t = 4.500$; $p = 0.004$) and without ($t = 3.674$; $p = 0.005$) ultrasound control of injection sites (Table 2).

Table 1

Clinical and demographic characteristics of patients with sialorrhea

Number of patients	19
Male to female ratio	14:5
Age (years); ($\bar{x}$ ± SD)	62 ± 17 (24–77)
Diagnosis of patients with sialorrhea	
Parkinson's disease (n)	13
Pantothenate kinase-associated neurodegeneration (n)	2
Multiple system atrophy (n)	2
Wilson's disease (n)	1
Post-operative sialorrhea (endarterectomy) (n)	1

Table 2

Response to botulinum toxin A (BTX-A) injections in parotid glands in patients with sialorrhea

Patients	Responders : non-responders		*p*
	Before the treatment	After the treatment	
All patients (n = 19)	–	13 : 6	
With ultrasound control (n = 7)	–	5 : 2	
Without ultrasound control (n = 12)	–	8 : 4	
Scores on UPDRS ADL drooling item			
All patients (n = 19)*	3.1 ± 0.1 (2-4)	1.8 ± 0.1 (0-3)	< 0.001
With ultrasound control (n = 7)*	2.9 ± 0.9 (2-4)	1.6 ± 0.9 (0-3)	0.004
Without ultrasound control (n = 12)*	3.2 ± 0.4 (3-4)	2.0 ± 0.8 (0-3)	0.005

UPDRS ADL – Unified Parkinson's Disease Rating Scale Activities of Daily Living; *values present means ± SDs with ranges in parentheses.

The mean dose of BTX-A per session was 104 ± 28 U (range: 64-140 U). In 13 patients who had beneficial response, it lasted approximately 3 months (2.9 ± 1.1 months; range 1–5 months). The time of the appearance of clinically relevant response was 7.9 ± 5.5 days (range 1–21 days).

Adverse effects were registered in 5 patients (26%) with dry mouth and mild swallowing difficulties being the most frequent.

Discussion

Although we did not use a very sensitive scale, we found beneficial effect of BTX-A injections on sialorrhea in approximately two thirds of the patients (68%), which is in accordance with the estimates of 69%–90% of responders in the previous studies [10–12]. Lim et al. [3] analyzed studies that included > 16 patients and identified 4 controlled studies, three of them being double blind, and only two of them randomized [6–8, 10]. Two studies reported significant improvement of drooling after BTX-A injections, one study found significant improvement in physical appearance and ease of caring for subjects, and one found no improvement in either frequency or severity of drooling [6, 8, 12, 13]. Lagalla et al. [14] described good response in 88% of BTX-A treated patients in comparison with 31% of those receiving placebo. Time to beneficial effect (between one and 21 days) and mean duration of the effect in our study (2.9 months) were similar as in other studies [11, 15].

Some authors suggested that therapeutic success might be achieved by injecting only submandibular glands, while other authors preferred combined administration to submandibular and parotid glands [8, 10, 12]. However, no study compared efficacy when different targets were injected. In our study we exclusively injected BTX-A to easily approached parotid glands in order to preserve adequate submandibular production of saliva which was necessary for dental caries prevention [16].

Lipp et al. [6] conducted double-blind, placebo controlled study on the efficacy of 3 different doses of BTX-A (Botox®; Allergan) and recommended a dose of 75 U, which proved to be more efficaceous than the smaller doses (37.5 U and 18.75 U). Lagalla et al. [14] administered 50 U of Botox® in every parotid gland, similar to Ellies et al. [16] The doses of Dysport® we used per session (104 U) were comparatively lower. It has been suggested that the usage of higher doses might result in better and longer-lasting response, but methodological differences between studies (including differences in injection sites) made it impossible to recommend the optimal mode of BTX-A application for sialorrhea with certainty [6].

The response in the patients who were injected with ultrasound guidance and those who were not sonographically guided was not different in our study, which contrasted Shetty at al. [17] who were giving low doses of Botox® (15 U) in each submandibular gland and recommended application only under ultrasound guidance. This difference may reflect an easiness to access the parotid glands.

Different studies used different subjective (visual analogue scales, quality of life questionnaries) and objective measures (salivatory gland scintigraphy, weight change of dental rolls after 5 minutes discontinuation of swallowing) that were used to assess BTX-A efficacy in sialorrhea [6, 8, 14]. However, Lipp et al. [6] reported discrepancy between the objective decrease of saliva production or reduction of drooling and changes in the quality of life measures. Therefore, in this study we decided to use the simple salivation item of the UPDRS part II (Activities of Daily Living).

The main limitation of our study was its open-labelled design. However, we believe that our results are still valuable considering: a rather large number of patients with different neurological disorders associated with sialorrhea; response achieved by injecting only parotid glands, data suggesting no necessity for ultrasound guidance in such apporach.

Conclusion

According to the results obtained, we suggest that BTX-A injections to easily accessible parotid glands are safe and efficaceous treatment for sialorrhea in different neurological disorders.

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