Toxicon 107 (2015) 129–140

Contents lists available at ScienceDirect

Toxicon

journal homepage: www.elsevier.com/locate/toxicon

Botulinum Toxin A and B in sialorrhea: Long-term data and literature overview

Martina Petracca [a, *, 1], Arianna Guidubaldi [a, 1], Lucia Ricciardi [a, b], Tàmara Ialongo [a], Alessandra Del Grande [a], Delia Mulas [a], Enrico Di Stasio [c], Anna Rita Bentivoglio [a]

[a] Institute of Neurology, Università Cattolica del Sacro Cuore, Rome, Italy
[b] Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College London, London, United Kingdom
[c] Institute of Biochemistry and Clinical Biochemistry, Università Cattolica del Sacro Cuore, Rome, Italy

ARTICLE INFO

Article history:
Received 30 July 2015
Received in revised form
17 August 2015
Accepted 24 August 2015
Available online 30 August 2015

Keywords:
Sialorrhea
Botulinum Toxin
Long-term treatment
Adverse effects
Parkinson's Disease
Amyotrophic Lateral Sclerosis

ABSTRACT

Introduction and objectives: In recent years, Botulinum Toxin has been shown to be efficacious and safe in the treatment of sialorrhea, but scanty data are available on its long term use. The aim of this study was to investigate adverse events, discriminate differences in safety, and evaluate the efficacy of long-term use of both abobotulinumtoxinA and rimabotulinumtoxinB ultrasound-guided injections for sialorrhea in a retrospective trial. Moreover we review the literature on this topic.

Patients and methods: Consecutive patients with severe sialorrhea and receiving at least two ultrasound-guided intrasalivary glands abobotulinumtoxinA 250 U or rimabotulinumtoxinB 2500 U injections were included. Clinical and demographic data were collected. Safety and tolerability were assessed on the basis of patients' self-reports. Efficacy was assessed by recording the duration of benefit and by the Drooling Severity Scale and Drooling Frequency Scale 4 weeks after intervention.

A review of literature was performed using 'Botulinum Toxin' and/or 'drooling' and/or 'sialorrhea' and/or 'hypersalivation' as keywords.

Results: Sixty-five patients (32 Amyotrophic Lateral Sclerosis and 33 Parkinson's Disease) were treated in a total of 317 sessions (181 rimabotulinumtoxinB and 136 abobotulinumtoxinA). Both serotypes induced a clear-cut benefit in 89% of injections. Mean benefit duration was 87 days (range 30–240), similar for abobotulinumtoxinA and rimabotulinumtoxinB but significantly shorter in Amyotrophic Lateral Sclerosis group compared to Parkinson's Disease ($p < 0.001$). Older age was positively correlated to benefit duration ($p = 0.003$). Botulinum Toxin-related and injection-related side effects complicated respectively 8,2% and 1,5% of treatments. The only Botulinum Toxin-related adverse event was a change of saliva thickness, mostly rated mild to moderate and more frequent in Amyotrophic Lateral Sclerosis patients ($p = NS$).

Conclusions: Both 250 U abobotulinumtoxinA and 2500 U rimabotulinumtoxinB administered by ultrasound-guided intrasalivary gland injection are safe and effective in treating sialorrhea, even in long-term follow-up. Older age is significantly associated with longer benefit duration. Parkinson's Disease patients showed a more favorable safety-efficacy ratio than did Amyotrophic Lateral Sclerosis patients, due to lower adverse events ($p = NS$) and longer benefit duration ($p < 0.001$).

1. Introduction

Sialorrhea is a common symptom of many neurological diseases (Benson and Daugherty, 2007). Botulinum Toxin (BoNT) injection for excessive drooling was first reported in 1997 (Bushara, 1997) and, in the last years, BoNT has emerged as a safe and effective treatment for drooling (Lim et al., 2006). Both BoNT A and B have been successfully and safely used (Chinnapongse et al., 2012;

Abbreviations: ALS, Amyotrophic Lateral Sclerosis; A/Abo, Abobotulinum; A/Ona, Onabotulinum; AEs, adverse effects; B/Rima, Rimabotulinum; BoNT, Botulinum Toxin; DFS, Drooling Frequency Scale; DSS, Drooling Severity Scale; PD, Parkinson's disease; SPSS, Statistical package for Social Science; USG, Ultrasound-guided.

* Corresponding author. Istituto di Neurologia, Policlinico Gemelli, largo A. Gemelli n° 8, 00168 Roma, Italy.
E-mail address: martina.petracca@gmail.com (M. Petracca).

[1] These authors equally contributed to the study.

http://dx.doi.org/10.1016/j.toxicon.2015.08.014
0041-0101/

Guidubaldi et al., 2011; Porta et al., 2001), however scanty data are available on long term follow up of repeated injections of BoNT into salivary glands.

Aim of this study is to present our long term data of BoNT treatment for sialorrhea, using two different BoNTs serotypes (Abobotulinum, A/Abo, Dysport® and Rimabotulinum, B/Rima, Neurobloc®) in patients with Parkinson's Disease (PD) and Amyotrophic Lateral Sclerosis (ALS) with a particular focus on safety and efficacy. Moreover we reviewed the literature on this topic, up to February 2014.

2. Patients and methods

All consecutive patients referred to our clinic who underwent ultrasound-guided (USG) intrasalivary glands BoNT injection for sialorrhea from October 2004 to March 2012, were included in the study. Most patients had been previously treated with anticholinergics without clinical improvement and/or with systemic side effects. Patients who received at least two USG intrasalivary glands BoNT-A (A/Abo 250 U, trade name: Dysport®; Ipsen, Slough, Berkshire, UK) or -B (B/Rima 2500 U, trade name: Neurobloc®; Solstice Neurosciences, LLC, Louisville, KY) injections, were included in the analysis.

Safety and tolerability were assessed on the basis of patients' self-reports.

Efficacy was assessed by means of: benefit duration (as stated by patients or by their caregivers) and changes of the Drooling Severity Scale (DSS) (range: 0–4) and Drooling Frequency Scale (DFS) (0–3) scores (Heine et al., 1996), 4 weeks after injection.

Statistical analysis was performed by means of the Statistical Package for Social Science (SPSS), release 15.0. Continuous variables were expressed as mean ± SD, categorical variables displayed as frequencies. Between-groups differences were compared with: Mann–Whitney or Kruskal–Wallis non parametric test for non-normally distributed continues variables and t-test or analysis of variance for normally distributed variables; categorical variables were compared using the $\chi 2$ test. Correlations were performed with the Pearson or Spearman correlation coefficient, as appropriate. Multiple linear regression with backward-stepwise method was also performed to investigate the relationship between mean benefit duration and age, gender, BoNT serotype, diagnosis type and number of treatments. Level of significance was set at a P value of 0.05.

A comprehensive literature search was conducted using Pubmed (from January 1999 to February 2014). The search terms were 'Botulinum toxin' and/or 'drooling' and/or 'sialorrhea' and/or 'hypersalivation'. The only limit was English language. The Cochrane Central Register of controlled trials was also considered, moreover references of studies were systematically searched to ensure the selection of all relevant studies, including retrospective ones. Papers without original data (meta-analysis and reviews) were excluded from this search.

As shown in Table 1, for each study were identified: diagnosis; number of treated patients and number of those who completed the trial; BoNT serotypes and dose; injected glands (parotid, submandibular, sublingual); USG; latency and duration; efficacy of the procedure; outcome measures (objective and/or subjective); percentage of responders; improvement as stated by the authors themselves; side-effects.

3. Results

Sixty-five patients were treated: 32 affected by ALS and 33 by PD. A total of 317 sessions (mean 5 for patient, range 2–16) were performed; 181 with B/Rima and 136 with A/Abo.

Mean age at the first treatment was 66 years (range 32–84), 69.4 for PD (range 40–84) and 62.9 for ALS patients (range 32–83), 63% were males. Mode of the ages at the first treatment was 70 years, 72 years for PD patients and 67 years for ALS patients. The mean follow-up period was 2.1 years (SD 1.4, range 1–8), in particular 2.6 years (SD 1.7, range 1–8) for PD patients and 1.7 (SD 0.9, range 1–5) for ALS patients. Fifty patients received at least 3 injections, twenty-seven five or more.

3.1. Safety and tolerability

Side effects data were gathered from the total number of treatments. The only BoNT related side effect was modification of saliva thickness in 26 injections (8.2%), with consequent dry mouth in 11 (3.5%: 9 after B/Rima and 2 after A/Abo, $p = 0.124$; 5 in PD and 6 in ALS patients, $p = 0.756$) and viscous saliva in 17 treatments (5.4%: 8 after B/Rima and 9 after A/Abo, $p = 0.454$; 7 in PD and 10 in ALS patients, $p = 0.459$). These side effects were more frequent among ALS (without reaching statistical significance), with no BoNT serotype-related difference.

Injection-related adverse effects (AEs) complicated 1.5% of treatments, unrelated to BoNT serotype or disease diagnosis: pain at injection sites (0.6%: 1 during A/Abo injection and 1 during B/Rima in two PD patients), subcutaneous hematoma (0.3%: 1 with B/Rima in one PD patient) and mouth bleeding (0.6%: 1 with B/Rima e 1 with A/Abo, in a PD patient and an ALS patient, respectively). No patients reported the burning sensation frequently caused by muscular injection of B/Rima (Colosimo et al., 2003; Tousi et al., 2004).

All side effects were transient and rated mild to moderate by the patients, with the exception of one case of severe dry mouth and two of troublesome viscous saliva, both reported by ALS patients. No patients reported dysphagia or facial weakness.

3.2. Efficacy

Compared to baseline, either A/Abo or B/Rima induced a clear-cut benefit in 89% of treatments (282 out of 317 injections); among 65 patients, at the end of the observation period, 28 (16 ALS and 12 PD) were lost at follow-up: 12 over 16 ALS patients died, 4 were bed-bound; considering the 12 PD patients 4 died, 3 refused to be re-injected after a treatment failure, 1 was bed-bound, 1 had a spontaneous remission (after clozapine withdrawal), and 3 were lost at follow-up.

In a multiple linear regression analysis, age and diagnosis resulted the only independent predictors of benefit duration. No association was found with gender, number of treatments or BoNT serotypes (Table 2). The overall mean duration was 87 days (SD 36.8, range 30–240), similar for both serotypes: 85 ± 35.7 days for A/Abo and 89 ± 37.7 days for B/Rima ($p = 0.392$) (Fig. 1). Repeated injections did not affect benefit duration ($p = 0.958$) (Fig. 2). Remarkably, age was positively related to benefit duration ($p = 0.003$) (Fig. 3) and benefit duration was significantly shorter in the ALS group (67.2 ± 25.5 days) than PD group (108.7 ± 35.3) ($p < 0.001$) (Fig. 4).

One month after injection (peak effect) the clinically significant improvement was evaluated as follows: the mean total improvement at DSS and DFS scale was calculated as the difference between the mean total score at first treatment time ($DSSt_0$ and $DFSt_0$) and the mean total score 4 weeks after injection ($DSSt_1$ and $DFSt_1$). Considering both treatment serotypes together, ($DSSt_0$–$DSSt_1$) was 2.2 ± 1.3 and ($DFSt_0$–$DFSt_1$) was 1.8 ± 0.7. Evaluating the single treatment serotype, after A/Abo ($DSSt_0$–$DSSt_1$) was 2 ± 0.8 and ($DFSt_0$–$DFSt_1$) was 1.7 ± 0.7 and after B/Rima ($DSSt_0$–$DSSt_1$) was 2.3 ± 1.6 and ($DFSt_0$–$DFSt_1$) was 1.8 ± 0.6. When considered