Parkinsonism and Related Disorders 30 (2016) 73–77

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Short communication

Drooling in Parkinson's disease: A randomized controlled trial of incobotulinum toxin A and meta-analysis of Botulinum toxins

Pushpa Narayanaswami [a, *], Thomas Geisbush [a, 1], Andrew Tarulli [a, 2], Elizabeth Raynor [a], Shiva Gautam [b], Daniel Tarsy [a], Gary Gronseth [c]

[a] Department of Neurology, Beth Israel Deaconess Medical Center/Harvard Medical School, BIDMC, 330 Brookline Ave, Boston, MA 02215, USA
[b] Department of Medicine, Beth Israel Deaconess Medical Center/Harvard Medical School, BIDMC, 330 Brookline Ave, Boston, MA 02215, USA
[c] Department of Neurology, Kansas University Medical Center, 3901 Rainbow Blvd, Mail Stop 1033, Kansas City, KS 66160, USA

ARTICLE INFO

Article history:
Received 9 May 2016
Received in revised form
19 June 2016
Accepted 4 July 2016

Keywords:
Parkinson's disease
Botulinum toxin
Sialorrhea
Clinical trials randomized controlled
Clinical trials systematic reviews/meta-analysis

ABSTRACT

Introduction: Botulinum toxins are a therapeutic option for drooling in Parkinson's Disease (PD). The aims of this study were to: 1. evaluate the efficacy of incobotulinum toxin A for drooling in PD. 2. Perform a meta-analysis of studies of Botulinum toxins for drooling in PD.
Methods: 1. Primary study: Randomized, double blind, placebo controlled, cross over trial. Incobotulinum toxin (100 units) or saline was injected into the parotid (20 units) and submandibular (30 units) glands. Subjects returned monthly for three evaluations after each injection. Outcome measures were saliva weight and Drooling Frequency and Severity Scale. 2. Systematic review of literature, followed by inverse variance meta-analyses using random effects models.
Results: 1. Primary Study: Nine of 10 subjects completed both arms. There was no significant change in the primary outcome of saliva weight one month after injection in the treatment period compared to placebo period (mean difference, gm ± SD: −0.194 ± 0.61, range: −1.28 to 0.97, 95% CI −0.71 to 0.32). Secondary outcomes also did not change. 2. Meta-analysis of six studies demonstrated significant benefit of Botulinum toxin on functional outcomes (effect size, Cohen's d: −1.32, CI −1.86 to −0.78). The other studies used a higher dose of Botulinum toxin A into the parotid glands.
Conclusions: This study did not demonstrate efficacy of incobotulinum toxin A for drooling in PD, but lacked precision to exclude moderate benefit. The parotid/submandibular dose-ratio may have influenced results. Studies evaluating higher doses of incobotulinum toxin A into the parotid glands may be useful.

1. Introduction

Sialorrhea or drooling is reported in approximately three-quarters of patients with Parkinson's disease (PD) and may cause aspiration, perioral chapping with secondary infection, dehydration, impaired speech, feeding difficulty, social embarrassment and decreased quality of life [1,2]. Salivary gland injections of Botulinum toxin (BoNT) have been evaluated for the treatment of drooling [2]. Previous studies vary in the type and dose of BoNT used, glands injected (parotid, submandibular or both), study duration and anatomic vs. ultrasound guided injections [3–10]. Incobotulinum Toxin A (Inco-A) (Xeomin®) is a purified BoNT A that contains neurotoxin without complexing proteins. It is equipotent to onabotulinum toxin A [11]. In this study we evaluate the safety and efficacy of injections of Inco-A into the parotid and submandibular glands for drooling in PD. To compare results of prior studies of BoNT we secondarily performed a meta-analysis of BoNT for drooling in PD.

* Corresponding author. Neurology TCC-8, BIDMC, 330 Brookline Ave, Boston, MA 02215, USA.
E-mail addresses: pnarayan@bidmc.harvard.edu (P. Narayanaswami), thomas.geisbush@my.rfums.org (T. Geisbush), Andrew.Tarulli@atlantichealth.org (A. Tarulli), eraynor@bidmc.harvard.edu (E. Raynor), sgautam@bidmc.harvard.edu (S. Gautam), dtarsy@bidmc.harvard.edu (D. Tarsy), ggronseth@kumc.edu (G. Gronseth).
[1] Present address: Rosalind Franklin University of Medicine and Science, 3333 Green Bay Rd, North Chicago, IL 60064, USA.
[2] Present address: Atlantic Neuroscience Institute, Overlook Medical Center, 99 Beauvoir Avenue, Summit, NJ 07901, USA.

http://dx.doi.org/10.1016/j.parkreldis.2016.07.001
1353-8020/

2. Methods

2.1. Study design (Fig. 1, CONSORT flow diagram)

This was a randomized, placebo controlled, cross-over trial with concealed allocation, approved by the Committee for Clinical Investigations at Beth Israel Deaconess Medical Center, Boston. (clinicaltrials.gov registration NCT01653132). Subjects provided written informed consent on an approved form. Subjects between 20 and 80 years of age with clinically diagnosed PD and troublesome drooling, swallowing function ≥5 on the Functional Oral Intake Scale (total oral intake of multiple consistencies requiring special preparation, or better) were included. Subjects previously treated for drooling had to have stopped medications at least 4 weeks before study entry; subjects who were on medications for drooling at the start of the study were maintained at stable doses through the study. Subjects on warfarin, with significant medical illnesses or neuromuscular transmission disorders, past use of BoNT, or cognitive impairment (≤23/30 on Mini Mental Status Exam) were excluded.

2.2. Evaluations

Unified Parkinson's Disease Rating Scale (UPDRS, Part 2 Questions 5,6,7 evaluating speech, salivation and swallowing and Part 3 questions 18 and 19 for motor examination of speech and facial expression), drooling frequency and severity score (DFSS) [2] and saliva weight (obtained by expectorating saliva into a pre-weighed cup for 5 min; mean of two trials). All evaluations were performed by investigators masked to the intervention (AT, ER).

2.3. Injection protocol

Inco-A, 100 units was reconstituted with 1 ml 0.9% sterile saline. Twenty units were injected into each parotid and 30 units to each submandibular gland using previously described techniques [10,12]. The same investigator (PN) performed all injections. Sterile, preservative free 0.9% saline, 1 ml, was used as placebo.

2.4. Timeline

Subjects were randomized by the study pharmacist using a computer generated schedule to receive either Inco-A or placebo, crossing over to the other intervention at the second injection. Subjects were evaluated at monthly intervals. At the end of three months, subjects entered a one month washout period. At the month 4 visit, if the saliva weight was ≥ (baseline- 0.5 SD), they received the second injection. Otherwise, they continued washout for another month and received the second injection at the month 5 visit. Subjects returned monthly for 3 more evaluations.

2.5. Outcome measures

Primary outcome: Difference in saliva weight at one month post-injection in the Inco-A period compared to the placebo period. Secondary outcomes, measured at the same time-point, were:

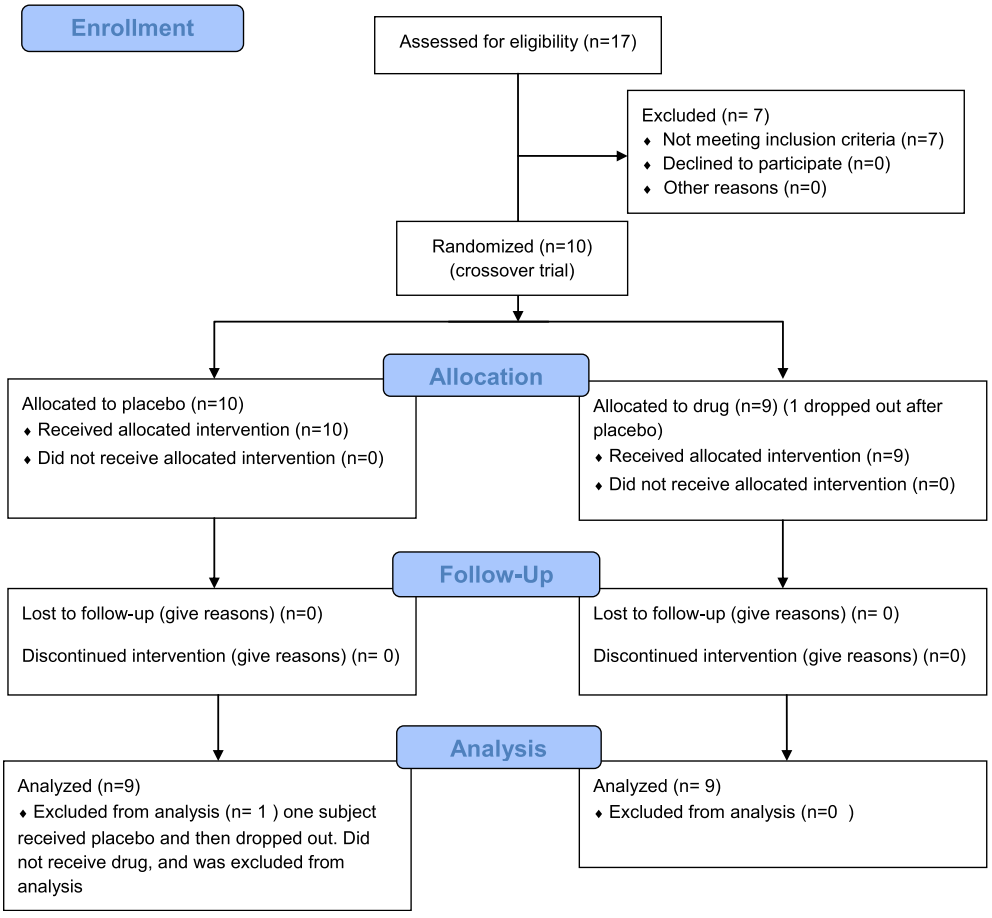

Fig. 1. CONSORT flow diagram. 17 subjects were screened for eligibility, of whom 7 were excluded. Ten subjects were randomized. One dropped out after the first injection.