Comparison of Efficacy and Immunogenicity of Original vs. Current BOTOX in Cervical Dystonia

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Abstract

Background: With long-term use and expanding indications for clinical use of botulinum toxin (BTX) there is a growing concern about the possibility of immunoresistance due to development of blocking antibodies. The actual frequency of immunoresistance in patients treated with repeat BTX injections, however, is not known. We postulate that as a result of lower protein load, the current BOTOX (5 ng of neurotoxin/100 units) should be less antigenic than the original preparation (25 ng of neurotoxin/100 units). **Objective:** To examine the hypothesis that BTX preparation with high protein content is associated with a higher frequency of antigenicity than the current preparation that has a relatively low protein content. **Methods:** We compared patients treated for cervical dystonia with original (used before 1998) BTX type A (BOTOX) (130 patients treated with both original and current BOTOX, 42 treated with only original BOTOX) and those treated only with the current (used since January 1998) BOTOX (n = 119). We used the mouse protection assay (MPA), considered the most reliable method for detecting blocking antibodies. **Results:** There was no significant difference in efficacy and adverse effects between the two preparations. Most importantly, MPA was more frequently abnormal in patients treated only with original BOTOX (4/42 or 9.5%) compared to those treated only with current (0/119) BOTOX ($p < 0.004$). Furthermore, a Cox regression survival analysis showed that the use of original BOTOX alone was more predictive of antibody formation than the current BOTOX, and the latter preparation decreased the risk of antibody formation by a factor of 6. **Conclusion:** In contrast to the original BOTOX, we have found no evidence of immunoresistance in patients treated with the current BOTOX for up to three years. We conclude that the low risk of antibody formation following current BOTOX treatment is at least in part related to lower protein loading.

Introduction

Focal chemodenervation produced by injection of botulinum toxin (BTX) represents an important advance in the treatment of a variety of movement as well as other neurologic and non-neurologic disorders. In 1989, BTX type A (BOTOX) was approved by the Food and Drug Administration for the treatment of blepharospasm and other facial spasms, and in 2000 for the treatment of cervical dystonia. The use of BTX, however, has rapidly expanded beyond these approved disorders and now includes a variety of ophthalmologic, gastrointestinal, urological, and cosmetic indications. With the growing and chronic use of BOTOX there is a possibility of increasing immunoresistance due to development of blocking antibodies. Some studies have suggested that up to 17% of patients treated repeated for cervical dystonia with BOTOX have immuno-resistance manifested by the presence of blocking antibodies. This figure and the published data on BOTOX related immunoresistance, however, is based on experience with the original preparation of BOTOX (lot 79-11), used prior to 1998, and there is virtually no published information about the antigenicity of the new BOTOX preparation, currently in use. Whereas the original BOTOX contained 25 ng of neurotoxin complex protein per 100 units, the current BOTOX contains only 5 ng of complex protein per 100 units. The primary goal of this study is to compare the efficacy, tolerability, and immunogenicity of the original versus the current BOTOX.

Methods

Over 2,500 patients have been treated with BOTOX in the movement disorder clinic at Baylor College of Medicine since 1983. Between 01-01-1995 and 01-31-2001 we treated and prospectively followed 249 patients with cervical dystonia. Of these patients, 130 were treated initially with the original BOTOX (n = 42) between 01-01-1995 and 12-31-1997 and 88 subsequently continued their treatment with the current BOTOX; 119 were treated only with the current BOTOX. All patients included in this study were injected by one of the movement disorder specialists (JJ) who assessed the patients at each visit, and rated their response according to previously published scale. The treating physician determined the dose and site of injection based on clinical assessment of patient's dystonia and associated abnormal posture and movement, complaints of muscle stiffness and pain, predominant muscle involvement determined by examination including palpation, head displacement, and previously established injection pattern. All clinical information was recorded in the BTX database and included: patient identification number, date of initial visit, date of each follow up visit, associated diagnoses, sites of injection, dose in mouse units (U) of BTX at each site, latency of response (days), peak effect (0 – 4 scale where 0 = no effect and 4 = marked improvement in severity and function), total duration of maximum effect (weeks), total duration of response (weeks), and complications. Presence of immunoresistance was assessed by the mouse protection assay (MPA), which has been previously described to correlate well with the presence of blocking antibodies. All patients who exhibited less than satisfactory response to their BTX injections (peak effect rating of 0 or 1) on two consecutive visits were tested for BTX antibodies by MPA. To minimize input variability, all data entry was performed by a single individual (JA) and all data points were verified by the data manager (KV), thus ensuring an accurate data set.

Results

The two preparations, the original and the current BOTOX, had similar efficacy (e.g. latency, peak effect, duration of response) [Fig. 1]. Although the total number of visits associated with adverse effects was slightly higher with the current BOTOX than with the original BOTOX, there was no difference in the frequency of types of side effects such as dysphagia, local pain, neck weakness, dry mouth or malaise between the two preparations [Fig. 2]. Blocking antibodies, as determined by positive MPA, were significantly more frequent in patients treated with the original BOTOX as compared to those treated with only current BOTOX (4/42 or 9.5% of patients treated only with the original BOTOX, $p < 0.004$, 5/130 or 3.8% of patient treated with both original and current BOTOX, $p < 0.061$) [Fig. 3].

Cox regression survival analysis, performed after adjusting for the covariate effects of age and cumulative dose, used to assess the likelihood of developing immunoresistance to BTX for those patients who received only original BOTOX (n = 42) or only current BOTOX (n = 119), showed that the use of original BOTOX alone was marginally more predictive of antibody formation than the use of current BOTOX alone when age and cumulative dose were statistically controlled ($p = 0.08$, odds ratio = 6.77, 95% CI odds ratio = 0.9 – 50.8). Thus, treatment with original BOTOX alone tended to increase the risk of antibody formation by a factor of 6 [Fig. 4].

Figure 1:

Efficacy of Original vs. Current BOTOX in Cervical Dystonia

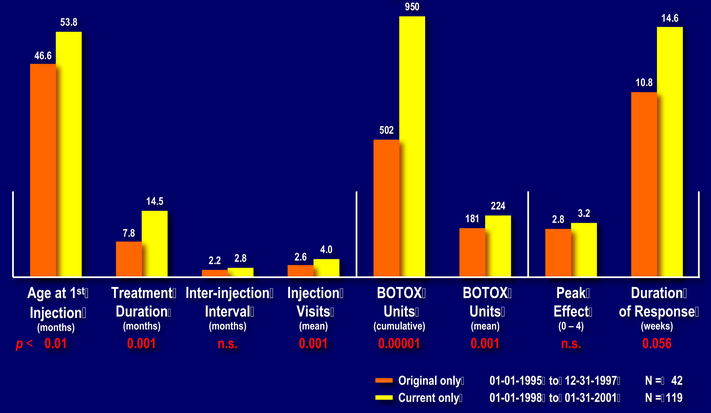


Figure 2:

Adverse Effect Profile of Original vs. Current BOTOX in Cervical Dystonia

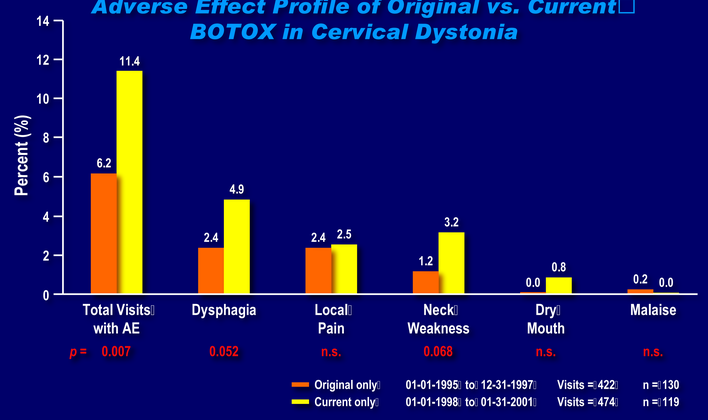


Figure 3:

Immunogenicity of Original vs. Current BOTOX in Cervical Dystonia

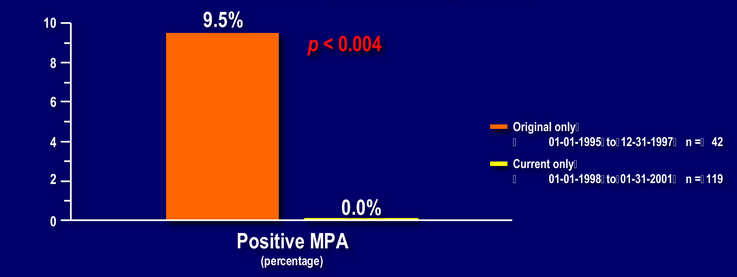
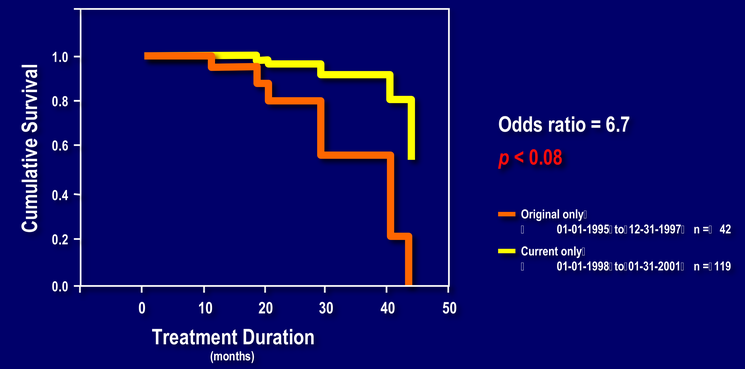


Figure 4:

Survival Without Evidence of Immunoresistance



Discussion

This is the first study that has longitudinally examined the effects of original versus current BOTOX. The primary aim of the study was to test the hypothesis that high protein load (25 ng/100 ml in original BOTOX) was associated with a higher risk of immunoresistance due to blocking antibodies than low protein load (5 ng/100 ml in current BOTOX).

To the extent that MPA measures blocking antibodies ("gold standard"), we found that 4/42 (9.5%) of patients treated only with original BOTOX had such antibodies whereas none of the patients treated only with the current BOTOX (n = 119) developed evidence of immunoresistance ($p < 0.004$).

The observation that 4 of 5 patients who developed antibodies were treated only with the original BOTOX and the one patient who was treated with both preparations received bulk of his treatments with original BOTOX provides strong evidence that the original BOTOX was markedly more antigenic than the current BOTOX. This finding, however, must be interpreted cautiously because this was not a controlled study and we did not systematically test all patients for BTX antibodies. Nevertheless, we believe that this finding is important because since January 1998 we have observed only three patients who satisfy the clinical criteria for secondary unresponsiveness as indicated by poor or no response to BOTOX (peak effect of 0 or 1) on two subsequent treatment visits, one of whom had abnormal unilateral brow injection (UBI), but none had positive MPA.

We believe that the lack of immunoresistance observed with current BOTOX is particularly notable because the group of patients treated with the current BOTOX was at a higher risk for developing antibodies since that the patients received a higher mean dose per visit, were treated for a longer period of time and had a higher number of treatment visits as compared to the group treated only with the original BOTOX. This suggests that the difference in the occurrence of immunoresistance is due to the fact that the current BOTOX contains 80% less neurotoxin complex protein than the original BOTOX and, therefore, is likely to be less antigenic.

Although there was no difference in the frequency of individual adverse effects between the original and current BOTOX, the slightly higher occurrence of overall side effects could be attributed to a significantly higher mean dose of current BOTOX per treatment visit. The higher dose could also possibly account for the observed longer duration of response with the current BOTOX.

In this long-term study, we have found no evidence of new immunoresistance attributed to the current BOTOX. With the introduction of the current BOTOX, the risk of inducing blocking antibodies has been reduced by a factor of 6. Thus, our study provides evidence that protein loading is an important risk factor for the development of immunoresistance.