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[Intervention Review]

Botulinum toxin type B for cervical dystonia

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ABSTRACT

Background

Cervical dystonia is the most common form of focal dystonia. It is characterized by involuntary posturing of the head and frequently is associated with neck pain. Disability and social withdrawal are common. Most cases of cervical dystonia are idiopathic and generally it is a life-long disorder. In recent years, Botulinum toxin type A (BtA) has become the first line therapy. However, some patients become resistant to it. This problem led to the study of another Botulinum toxin (Bt) serotype, Bt type B (BtB) to address the issues of clinical efficacy, effect size, and safety of BtB in the treatment of cervical dystonia.

Objectives

To determine whether botulinum toxin (BtB) is an effective and safe treatment for cervical dystonia.

Search methods

We identified studies for inclusion in the review using the Cochrane Movement Disorders Group trials register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE; and by handsearching the Movement Disorders Journal and abstracts of international congresses on movement disorders and botulinum toxin, by communication with other researchers in the field, by searching reference lists of papers found using the above search strategies, and by contacting authors and drug manufacturers.

Selection criteria

We considered studies eligible for inclusion in the review if they evaluated the efficacy of BtB for the treatment of cervical dystonia in randomized, placebo-controlled trials.

Data collection and analysis

We used a paper pro forma to collect data from the included studies with double extraction by two independent reviewers. Both reviewers assessed each trial for internal validity and settled differences by discussion.
The outcome measures used included adverse events, improvement in symptomatic rating scales, subjective evaluation by patients and clinicians, changes in pain scores, changes in quality of life assessments.

Main results

Studies were short term (16 weeks) employing a single BtB injection session. All were multicentre and conducted in the US. All patients included had previously received BtA. The trials differed with respect to whether or not the patients were still responding to BtA but other entry criteria were similar. All studies used a dose of 10,000 Units of BtB in one group and the technique of administration was the same. Meta-analysis of three trials enrolling 308 participants showed statistically and clinically significant improvements in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total score at week four with a Peto odds ratio (OR) for the number of patients who had at least

a 20% improvement of 4.69 (95% CI 2.06 to 10.69) and a weighted mean difference of -5.92 (95% CI -9.61 to -2.23). Subjective rating scales (Patient Global Assessment of Change, Investigator Global Assessment of Change, and Patient Analog Pain Assessment) also improved. Adverse events clearly associated with the mechanism of action of BtB included dysphagia and dry mouth and the number of patients with any adverse event were more frequent in BtB treatment groups. Subgroup analyses showed a clear dose-response relationship for subjective and objective benefit, for frequency and severity of adverse events, and a greater benefit for BtA resistant patients than BtA responders in the primary outcome. The duration of effect was about 16 weeks.

We found three eligible studies enrolling 308 participants. Studies were short term (16 weeks) employing a single BtB injection session. All were multicentre and conducted in the US. All patients included had previously received BtA. The trials differed with respect to whether or not the patients were still responding to BtA but other entry criteria were similar. Patient groups were appropriately selected and well matched. From the methodological point of view these trials were probably not subjected to important selection, performance or attrition bias and all studies used an intention-to-treat analysis.

The dose varied significantly between studies although all used 10,000 Units of BtB in one group and the technique of administration was the same. The primary outcome in all trials was change in TWSTRS total score at week four and other efficacy outcomes were similar between studies. The number of dropouts was small and balanced in all trials. Reasons for withdrawals were given. One randomized double-blind placebo-controlled study was excluded because data couldn't be extracted for the outcomes.
Meta-analysis showed statistically and clinically significant improvements with a Peto odds ratio (OR) of 20% in TWSTRS total score at week four (OR 4.69; 95% CI 2.06 to 10.69) and a weighted mean difference of -5.92 (95% CI -9.61 to -2.23). Subjective rating scales (Patient Global Assessment of Change, Investigator Global Assessment of Change, and Patient Analog Pain Assessment) also improved. The weighted mean difference for changes in these subjective scales varied between -13% to -21%. However, for many of the outcomes, we could not combine data from all studies. Only adverse events clearly associated with the mechanism of action of BtB were more frequent in the treatment group. These included dysphagia and dry mouth. The number of patients with any adverse event was more frequent with BtB. Subgroup analyses showed a clear dose-response relationship for subjective and objective benefit and for frequency and severity of adverse events. Subgroup analyses showed a greater benefit for the BtA resistant patients than BtA responders in the primary outcome. The duration of effect was about 16 weeks. These trials did not measure quality of life nor did they establish the long term duration of effect or immunogenicity

Authors' conclusions

A single injection of BtB was effective and safe for treating cervical dystonia. Long-term uncontrolled studies suggested that further injection cycles continue to work for most patients.

Future research should explore technical factors such as the optimum treatment intervals and use of image or electromyographic guidance for administration. Other issues include service delivery, quality of life, long-term efficacy and safety, and the relative indications for BtA, BtB and other treatments such as deep brain stimulation

PLAIN LANGUAGE SUMMARY

Botulinum toxin type B for cervical dystonia or involuntary positioning of the head

Cervical dystonia is the most common form of focal dystonia and is characterized by involuntary posturing of the head. It is frequently associated with neck pain and may lead to physical disability and social withdrawal. Botulinum toxin type A (BtA) has become the first line therapy but some patients become resistant to this drug. Another serotype of Botulum toxin, type B (BtB) has been developed. Three randomized controlled studies of a single intramuscular injection of BtB (up to a dose of 10,000 Units) showed improvements in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total score, which includes measures of disability, severity and pain, and patient assessed measures four weeks after injection and lasting about 16 weeks, even in patients resistant to BtA. Adverse events associated with how the drug works included difficulty in swallowing (dysphagia) and dry mouth.