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Herd CP, Tomlinson CL, Rick C, Scotton WJ, Edwards J, Ives N, Clarke CE, Sinclair A. Botulinum toxins for the prevention of migraine in adults. Cochrane Database of Systematic Reviews 2018, Issue 6. Art. No.: CD011616. DOI: 10.1002/14651858.CD011616.pub2.

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[Intervention Review]

Botulinum toxins for the prevention of migraine in adults

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Editorial group: Cochrane Pain, Palliative and Supportive Care Group. **Publication status and date:** New, published in Issue 6, 2018.

Citation: Herd CP, Tomlinson CL, Rick C, Scotton WJ, Edwards J, Ives N, Clarke CE, Sinclair A. Botulinum toxins for the prevention of migraine in adults. *Cochrane Database of Systematic Reviews* 2018, Issue 6. Art. No.: CD011616. DOI: 10.1002/14651858.CD011616.pub2.

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ABSTRACT

Background

Migraine occurs in around 15% of adults and is ranked as the seventh most disabling disease amongst all diseases globally. Despite the available treatments many people suffer prolonged and frequent attacks which have a major impact on their quality of life. Chronic migraine is defined as 15 or more days of headache per month, at least eight of those days being migraine. People with episodic migraine have fewer than 15 headache days per month. Botulinum toxin type A has been licensed in some countries for chronic migraine treatment, due to the results of just two trials.

Objectives

To assess the effects of botulinum toxins versus placebo or active treatment for the prevention or reduction in frequency of chronic or episodic migraine in adults.

Search methods

We searched CENTRAL, MEDLINE & MEDLINE in Process, Embase, ClinicalTrials.gov and World Health Organization International Clinical Trials Registry (to December 2017). We examined reference lists and carried out citation searches on key publications. We sent correspondence to major manufacturers of botulinum toxin.

Selection criteria

Randomised, double-blind, controlled trials of botulinum toxin (any sero-type) injections into the head and neck for prophylaxis of chronic or episodic migraine in adults. Eligible comparators were placebo, alternative prophylactic agent or different dose of botulinum toxin.

Data collection and analysis

Two review authors independently selected trials and extracted data. For continuous outcomes we used mean change data when available. For dichotomous data we calculated risk ratios (RRs). We used data from the 12-week post-treatment follow-up time point. We assessed the evidence using GRADE and created two 'Summary of findings' tables.

Main results

Description of trials



We found 90 articles describing 28 trials (4190 participants), which were eligible for inclusion. The longest treatment duration was three rounds of injections with three months between treatments, so we could not analyse long-term effects. For the primary analyses, we pooled data from both chronic and episodic participant populations. Where possible, we also separated data into chronic migraine, episodic migraine and 'mixed group' classification subgroups. Most trials (21 out of 28) were small (fewer than 50 participants per trial arm). The risk of bias for included trials was low or unclear across most domains, with some trials reporting a high risk of bias for incomplete outcome data and selective outcome reporting.

Botulinum toxin versus placebo

Twenty-three trials compared botulinum toxin with placebo. Botulinum toxin may reduce the number of migraine days per month in the chronic migraine population by 3.1 days (95% confidence interval (CI) -4.7 to -1.4, 4 trials, 1497 participants, low-quality evidence). This was reduced to -2 days (95% CI -2.8 to -1.1, 2 trials, 1384 participants; moderate-quality evidence) when we removed small trials.

A single trial of people with episodic migraine (N = 418) showed no difference between groups for this outcome measure (P = 0.49).

In the chronic migraine population, botulinum toxin reduces the number of headache days per month by 1.9 days (95% CI -2.7 to -1.0, 2 trials, 1384 participants, high-quality evidence). We did not find evidence of a difference in the number of migraine attacks for both chronic and episodic migraine participants (6 trials, N = 2004, P = 0.30, low-quality evidence). For the population of both chronic and episodic migraine participants a reduction in severity of migraine rated during clinical visits, on a 10 cm visual analogue scale (VAS) of 3.3 cm (95% CI -4.2 to -2.5, very low-quality evidence) in favour of botulinum toxin treatment came from four small trials (N = 209); better reporting of this outcome measure from the additional eight trials that recorded it may have improved our confidence in the pooled estimate. Global assessment and quality-of-life measures were poorly reported and it was not possible to carry out statistical analysis of these outcome measures. Analysis of adverse events showed an increase in the risk ratio with treatment with botulinum toxin over placebo 30% (RR 1.28, 95% CI 1.12 to 1.47, moderate-quality evidence). For every 100 participants 60 experienced an adverse event in the botulinum toxin group compared with 47 in the placebo group.

Botulinum toxin versus other prophylactic agent

Three trials studied comparisons with alternative oral prophylactic medications. Meta-analyses were not possible for number of migraine days, number of headache days or number of migraine attacks due to insufficient data, but individually trials reported no differences between groups for a variety of efficacy measures in the population of both chronic and episodic migraine participants. The global impression of disease measured using Migraine Disability Assessment (MIDAS) scores were reported from two trials that showed no difference between groups. Compared with oral treatments, botulinum toxin showed no between-group difference in the risk of adverse events (2 trials, N = 114, very low-quality evidence). The relative risk reduction (RRR) for withdrawing from botulinum toxin due to adverse events compared with the alternative prophylactic agent was 72% (P = 0.02, 2 trials, N = 119).

Dosing trials

There were insufficient data available for the comparison of different doses.

Quality of the evidence

The quality of the evidence assessed using GRADE methods was varied but mostly very low; the quality of the evidence for the placebo and active control comparisons was low and very low, respectively for the primary outcome measure. Small trial size, high risk of bias and unexplained heterogeneity were common reasons for downgrading the quality of the evidence.

Authors' conclusions

In chronic migraine, botulinum toxin type A may reduce the number of migraine days per month by 2 days compared with placebo treatment. Non-serious adverse events were probably experienced by 60/100 participants in the treated group compared with 47/100 in the placebo group. For people with episodic migraine, we remain uncertain whether or not this treatment is effective because the quality of this limited evidence is very low. Better reporting of outcome measures in published trials would provide a more complete evidence base on which to draw conclusions.

PLAIN LANGUAGE SUMMARY

Botulinum toxin injections for preventing migraine in adults

Bottom line

People with chronic (persisting) migraine treated with botulinum toxin injections had two fewer migraine days per month than people treated with placebo (fake treatment). It is unclear if this improvement was large enough to make a meaningful difference to their lives. More work is needed to show whether botulinum toxin is better than oral treatments (treatments that are swallowed), that prevent migraine. The evidence for botulinum toxin for people with episodic (occasional) migraine was uncertain. Treatment with botulinum toxin did not cause many side effects.



Background

Migraine occurs in three in 20 adults and three in every four sufferers are female. People who have 15 or more days of headache in a month, with eight or more of those days being migraine, have chronic migraine. People with fewer than 15 days of headache in a month have episodic migraine. We included trials that compared botulinum toxin treatment with placebo injections of salt water, different doses of botulinum toxin, or other oral treatments to prevent migraine. We collected information for the following outcomes: number of migraine days in a month (our preferred measure); migraine severity; use of medications for migraine symptoms; disease-rating scales; quality-of-life scales; side effects; and cost effectiveness of treatment.

Trial characteristics

We found 28 clinical trials involving 4190 participants. Their average age was 42 years and eight in 10 were female. It is likely that we found all relevant trials published before December 2017. Trials were short, the longest lasting nine months. Around half the participants had chronic migraine symptoms and half episodic. Trial doses ranged from 6 to 300 units. The dose recommended for chronic migraine in the UK and USA is 155-195 units. Sixteen trials, involving 8 in 10 participants, were funded by botulinum toxin manufacturers.

Key results

Disappointingly, there was not enough detail in the trial reports about many important measures of disease for us to study them.

People with chronic migraine treated with the recommended dose of botulinum toxin had two fewer migraine days in a month than people treated with placebo. Six trials in both chronic and episodic migraine also reported the number of migraine attacks per month. Botulinum toxin was not proven to be better than placebo at reducing the number of attacks suffered per month. Botulinum toxin may reduce the severity of migraines but we need larger trials to have confidence in this result.

Three trials also compared botulinum toxin (at least 100 units) with oral treatments (sodium valproate and topiramate). There was no difference in the improvement in number of days with migraine; these data came from one trial. Botulinum toxin was no better or worse than oral treatments at reducing the scores on a migraine disability questionnaire (Migraine Disability Assessment) for people with chronic migraine. As all the results for comparison with oral treatments came from a few small trials it is likely that further large trials would change these results and so we cannot be confident in them.

Of the participants treated with botulinum toxin, 60 in 100 reported side effects (most common was drooping eyelid or muscle weakness), which was a little higher than the number receiving placebo (47 in 100). No difference was seen in the risk of side effects between botulinum toxin and oral treatments. Participants from two small trials were nearly four times less likely to stop their treatment if they were given botulinum toxin than if they had oral treatments. Information about side effects was reported for 8 in 10 trial participants.

Quality of the evidence

We rated the quality of the evidence from trials using four levels: very low, low, moderate or high. Very low-quality evidence means that we are very uncertain about the results. High-quality evidence means that we are very confident in the results. The results for the change in migraine days for people with chronic migraine and the number of side effects experienced were based on moderate-quality evidence. All other results discussed in this summary were low or very low-quality evidence, so the true effect is likely to be different to these results.