Efficacy of botulinum toxin type A for the prophylaxis of episodic migraine headaches: a meta-analysis of randomized, double-blind, placebo-controlled trials

CRD summary
The review found that there was no statistically significant difference between botulinum toxin type A and placebo in the prophylaxis of episodic migraine. Despite the some minor flaws in the conduct and reporting of the review, the authors' conclusion appears to be reliable.

Authors' objectives
To evaluate the efficacy of botulinum toxin type A for the prophylaxis of episodic migraine headaches.

Searching
PubMed and the Cochrane Library were searched from inception to October 2007 for publications in any language. Search terms were reported. Google Scholar was also searched. Bibliographies of each retrieved article were handsearched.

Study selection
Randomised double-blind, placebo-controlled trials that compared the efficacy of peri-cranial botulinum toxin A injections with placebo for the prevention of migraines in patients (with a history of episodic migraine headaches) were eligible for inclusion. Studies that involved subgroup analysis were excluded. Patients with episodic migraines were defined as those with fewer than 15 headaches in a month, over a three month period. The primary outcome was change from baseline in migraine frequency.

The dose of botulinum toxin A used in the included trials varied from 7.5 to 260U; the sites of injection also varied. Concomitant episodic drugs were allowed in most trials. There was little data relevant to the placebos used.

The mean age of included participants was 43 years (range 38.3 to 45.3 years); the majority of patients were female. The mean number of migraines per month was 5.3 (range 4.4 to 6.5); the mean number of years since diagnosis of migraine was 21.2 years (range 15.6 to 23.9 years).

All trials excluded patients who were potentially allergic to botulinum toxin or taking drugs likely to provoke adverse drug interactions with botulinum toxin A, pregnant women, or those planning pregnancy during the trial.

Two independent reviewers performed the selection, with disagreements resolved by consensus.

Assessment of study quality
Three reviewers independently assessed methodological quality assessment using the Downs and Black checklist, with disagreements resolved by consensus. The checklist covered the following criteria: external validity, internal validity bias, selection bias, trial power and reporting. A score of under 50% was weak, 50 to 69% fair, 70 to 79% good, and 80 to 100% very good quality.

Data extraction
Mean changes with standard deviation in headache frequency were extracted, with 95% confidence intervals (CI), for 30, 60, and 90 days after treatment. If the standard deviation was not reported for an individual trial, a pooled standard deviation for the remaining trials was calculated and applied. Some trials provided data for subgroups, including different doses of botulinum toxin A, and placebo response and non-response.

Two independent reviewers extracted data, with disagreements resolved by consensus and a third reviewer acting as adjudicator.
Methods of synthesis
Meta-analyses of standardised mean difference (Cohen's d) were calculated using a random-effects model, for 30, 60 and 90 days after treatment, where an effect size of less than 0.2 was considered small.

Meta-analyses were also performed for high dose (up to 100U) and low dose (under 100U) botulinum toxin A or placebo treatment, at 30, 60 and 90 days after treatment, and also after removal of patients who responded to placebo, or those who did not, from the dataset. Between trial heterogeneity was determined using $\chi^2$ and $I^2$ tests.

Results of the review
Eight relevant randomised controlled trials (RCTs) were identified (n=1,601 participants, sample size 30 to 495). The mean quality checklist score was 67.3% (range 50 to 81.3%). The mean loss to follow-up was 2.7% (range 0 to 4.1%).

There were no statistically significant differences in overall treatment effect size on migraine frequency for botulinum toxin A compared to placebo at 30 days ($d -0.06, 95\%CI -0.14$ to 0.03), 60 days ($d -0.05, 95\%CI -0.14$ to 0.03), and 90 days ($d -0.05, 95\%CI -0.13$ to 0.04).

Meta-analyses for high dose compared to placebo and low dose treatment compared to placebo, at 30, 60 and 90 days, found that there was no statistically significant difference in treatment effect size at any time point. There was a non-significant trend for high dose treatment to be less effective over time and a non-significant trend for low dose treatment to be more effective over time. Meta-analyses after removal of either patients who responded to placebo, or those who did not, from the dataset also found no significant effect on migraine frequency.

There was no significant heterogeneity for all the meta-analyses.

Authors' conclusions
Botulinum toxin A was not significantly different from placebo for the prophylactic treatment of episodic migraine headaches, both from a clinical and a statistical perspective.

CRD commentary
The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched with no language restrictions, but the authors considered that some non-English articles may have been missed. Additionally, unpublished studies were not considered and the authors did not report whether publication bias was assessed. Trial quality was assessed using suitable criteria. Efforts were made to reduce error and bias throughout the review process.

Trial details were reported, but the specific botulinum toxin A doses used in each trial were not presented. The authors recognised that the cut-off point for a high and low botulinum toxin A dose was arbitrary, and that double-blind treatment was difficult to achieve with the active intervention, but any overestimated effects were unlikely to have affected the authors’ conclusion. Statistical heterogeneity was assessed. The statistical method used for the meta-analysis of the RCTs seemed appropriate; relevant subgroup analyses were performed.

Despite the some minor flaws in the conduct and reporting of the review, the authors’ conclusion appears to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors identified a need for large multi-centre studies using consistent doses of botulinum toxin A and injection sites with enhanced consistency of comparison variables, and suggested that studies should focus on smaller doses rather than doses of over 100U. They also recommended that future research should also evaluate the effect of...
botulinum toxin A on other forms of migraine, such as chronic migraine. Unpublished material should be included in future systematic reviews.

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