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Review article

Pharmacological interventions for treating sialorrhea associated with neurological disorders: A mixed treatment network meta-analysis of randomized controlled trials

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ABSTRACT

Sialorrhea is a common distress associated with certain neurological disorders. The aim of this study is to compare the pharmacological agents used for treating sialorrhea by network meta-analysis. Electronic databases were searched for randomized clinical trials comparing active drugs with either placebo or other active drugs. Total drooling scores was the primary outcome measure. Inverse variance heterogeneity model was used for both direct and mixed treatment comparison analysis. Twenty one studies were included in the systematic review and 15 in the meta-analysis. Compared to placebo, benztropine, botulinum toxins A and B are associated with a significant reduction in the frequency and severity of drooling both in the overall neurological disorders as well as for children with cerebral palsy. Only botulinum toxin A and B were associated with significant therapeutic effects in Parkinson's disease. Benztropine and botulinum toxins A and B were observed to be effective in reducing sialorrhea associated with neurological disorders.

1. Introduction

Sialorrhea is excessive salivation associated with neurological disorders or localized anatomical abnormalities in the oral cavity [1]. The neurological disorders associated with sialorrhea include cerebral palsy, neurological disorders in children, Parkinson's disease, amyotrophic lateral sclerosis and stroke in adults [2]. Nearly 40% of children with cerebral palsy and 80% of adults with Parkinson's disease have been reported to have sialorrhea [3]. Excessive production and drooling of saliva may impair mastication and speech and can result in humiliation and thus associated with a poor quality of life.

Pharmacological agents such as Botulinum toxins, glycopyrrolate, scopolamine and benztropine have been shown in several individual clinical trials to be useful in treating sialorrhea [4,5]. Of these, the botulinum toxin is injected into the salivary gland guided either by anatomical external palpation or ultrasound, while all other agents are administered in an oral or parenteral form [6]. A direct pairwise meta-analysis comparing only botulinum toxins (both A and B) in sialorrhea has been published [7]. Head-to-head clinical trials comparing other pharmacological interventions are lacking precluding any interpretation on their relative effects. A mixed treatment comparison network meta-analysis compares the interventions through a common comparator and hence the effect estimates of the interventions in the absence of overt head-to-head clinical trials can be obtained [8]. We conducted the present network meta-analysis to compare the available pharmacological interventions to treat sialorrhea.

2. Patient and methods

2.1. Information source and search strategy

The protocol of this review was registered with PROSPERO with the identification number CRD42017069223. We did a thorough literature search in the Cochrane CENTRAL and Medline (through PubMed) with the following search strategy: (botulinum toxin [tiab] OR biperiden [tiab] OR botulinum toxin [tiab] OR ipratropium [tiab] OR glycopyrrolate [tiab] OR benztropine [tiab] OR scopolamine [tiab] OR tropicamide [tiab]) AND (sialorrhea [tiab] OR ptyalis [tiab] OR drooling [tiab]). We did not place any limits to either publication year or language.

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2.2. Eligibility criteria

We included randomized controlled clinical trials conducted in adults or children, presenting with sialorrhea due to any neurological disorder such as cerebral palsy, Parkinson's disease, amyotrophic lateral sclerosis and stroke. We excluded studies that recruited patients with sialorrhea associated with the use of antipsychotics. The interventions assessed include botulinum toxins (A and B), glycopyrrolate, ipratropium, scopolamine, tropicamide and benztropine compared to either placebo or without any active intervention. We also included studies that compared the active agents amongst themselves but excluded studies that compared the drugs either with radiotherapy or complementary and alternative medicine. Total drooling score was the primary outcome. Number and weight of bibs or dental rolls used, change in the drooling scores from the baseline and adverse events were considered as secondary outcome measures.

2.3. Study procedure and statistical analyses

Two authors performed an independent literature search with the above mentioned search strategy and extracted the following data: trial site, year, trial methods, participants, interventions, and outcomes. Any disagreement between the authors was resolved through discussion. We carried out and reported the present network meta-analysis according to the preferred reporting items in systematic review and meta-analysis (PRISMA) guidelines. [9] The risk of bias of the included studies was assessed using Cochrane risk of bias tool. [10] We intended to analyze publication bias, but considering the less numbers of studies included for each comparison, this could not be performed. Cohen's standardized mean difference [95% confidence interval] was considered as the effect estimate for numerical outcomes and odds ratio [95% confidence interval] for the categorical outcome variables. Inconsistency between direct and indirect pooled effect estimates by $\bar{H}$ statistics wherein a value of <3 was considered as minimal, 3–6 as modest and >6 as gross [11]. We carried out sub-group analysis for the primary outcome variable according to the specific diagnoses of the study participant viz. cerebral palsy, Parkinson's disease and amyotrophic lateral sclerosis. We also carried out trial sequential analysis to adjust the pooled estimates according to the information size achieved till date. Obrien-Fleming method of alpha-spending function was used to assess the statistical significance of the pooled estimate in relation to the information size that has been achieved till date. We used MetaXL for the analyses of pooled estimates through mixed treatment comparisons and trial sequential analysis software for analyzing the adjusted pooled estimates [12,13]. Grading of the evidence for key comparisons were carried out using Grades of Recommendation, Assessment, Development and Evaluation (GRADE) working group approach [10].

3. Results

3.1. Search results

A total of 279 articles were obtained with the above mentioned search strategy of which 21 [14–34] were included in the systematic review and 15 [14–28] in the network meta-analysis. The PRISMA flow diagram for the study is depicted in Fig. 1. The key characteristics of the included studies are mentioned in the Online Supplementary Table 1. Risk of bias of the individual studies is depicted in Fig. 2. Most of the studies were observed to have low risk of bias in all the domains. The network plot of the interventions assessed for the primary outcome variable is depicted in the Online Supplementary Fig. 1.

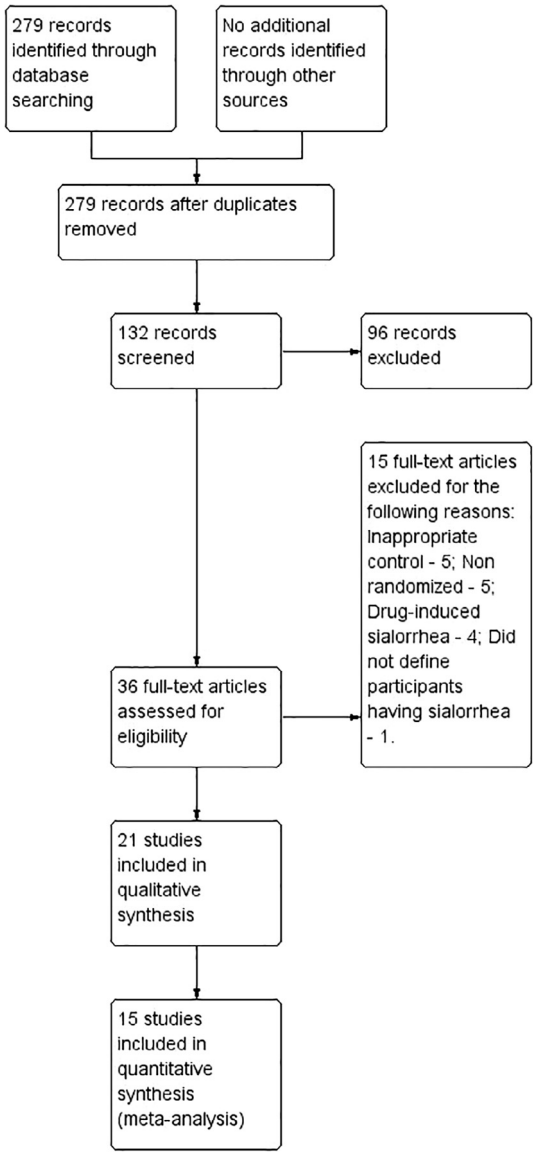

Fig. 1. PRISMA flow diagram. A total of 21 studies were included in the systematic review and 15 in the network meta-analysis.

3.2. Pooled results

3.2.1. Primary outcome variable

Data from 12 studies on 360 participants was used to analyze the difference in the primary outcome variable between the interventions. Three studies each compared botulinum toxin A and glycopyrrolate with placebo, four compared botulinum toxin B with placebo and one each compared benztropine with placebo and botulinum toxin A and B. Forest plot for comparisons of the pooled estimates by mixed treatment comparison approach revealed a statistically significant reduction in the total drooling scores with benztropine, botulinum toxin A and B compared to placebo (Fig. 3). No inconsistencies were observed between the direct and indirect estimates ($\bar{H} = 1$). Table 1 summarizes the pooled estimates of direct and mixed treatment comparisons between the interventions and it can be observed that benztropine performs better than botulinum toxin A and B and glycopyrrolate. Benztropine has the highest probability of being 'the best' in the pool occupying the top position in the Forest plot (Fig. 3).