Review Article

Systematic Review of the Effectiveness of Botulinum Toxin or Radiotherapy for Sialorrhea in Patients with Amyotrophic Lateral Sclerosis

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Abstract

Fifty percent of patients with amyotrophic lateral sclerosis (ALS) experience problems handling serous saliva and 20% fail to achieve adequate control of sialorrhea with anticholinergic medications, or experience intolerable adverse effects from these drugs. Both botulinum and radiotherapy have been suggested in the literature as treatments for intractable sialorrhea. In this review, we assess the evidence for the effectiveness and toxicity of botulinum toxin and radiotherapy for sialorrhea in patients with ALS. Relevant studies were retrieved from Medline, Embase and Cochrane Databases. Handsearching of Neurology, Journal of Pain and Symptom Management, *and* Palliative Medicine *and of reference lists, was carried out. Five studies (28 patients) were included in the analysis of botulinum. Of the four studies using an intraglandular method of injection, no adverse effects occurred. Two of these had positive findings of the effect of botulinum in salivary secretion rate and quality of life. In contrast, significant adverse effects were experienced by two patients in a study of retrograde injections into the salivary ducts. Two studies were included in the analysis of radiotherapy (27 patients). Both demonstrated a positive effect of radiotherapy on salivary secretion rate. Some patients experienced mild acute side effects. Because of the small numbers of studies, small sample sizes, and poor quality of reporting, it is not possible to draw firm conclusions. There is some evidence indicating that both botulinum and radiotherapy are well tolerated, effective treatments for persistent sialorrhea in patients with ALS and that the duration of action is up to three months with botulinum and six months with radiotherapy.* J Pain Symptom Manage 2009;37:246–258.

Key Words

Amyotrophic lateral sclerosis, motor neurone disease, sialorrhea, drooling, botulinum, radiotherapy

Background

Amyotrophic lateral sclerosis (ALS) is a disease of both upper and lower motor neurons. Its prevalence is 4–6 per 100,000 population.[1] The mean age of onset is 56 years and it is

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more common in males than females. In early stage disease, features of either bulbar or spinal disease predominate, but as the disease progresses, typically both become evident. Median survival in the bulbar form of the disease is 20 months and in the spinal form 29 months.[2] The only specific treatment that may modestly improve survival is riluzole, a glutamate antagonist. Patients with ALS should receive regular support from a multidisciplinary team,[3] with the goal of maintaining nutritional status and respiratory function, and symptomatic management of pain, emotional lability, depression, spasticity, cramps, and sialorrhea.

Patients with bulbar palsy experience problems handling serous saliva and mucous nasal and bronchial secretions as a result of poor lip closure, head position, and weakness of bulbar muscles. The management of mucous bronchial secretions differs from that of serous salivary secretions. Approximately 1.5 L of saliva is produced per day. In the fasting state, the paired submandibular glands produce 70% of saliva; the sublingual glands produce 5%; and the parotid glands produce 20%. Stimulated salivary production is mainly by the parotid glands. Inability to swallow saliva causes drooling or sialorrhea, which can lead to maceration of skin, soaking of clothes, and exacerbation of dysarthria. It can also cause psychosocial distress and social embarrassment.

Secretory innervation to the salivary glands is mainly via parasympathetic nerves. The mainstay of management of sialorrhea in ALS is use of anticholinergic medications. However, some patients have an inadequate response to these medications or experience intolerable adverse effects. Alternative treatments, namely injections of botulinum toxin and radiotherapy, have been suggested in the literature. Botulinum blocks presynaptic release of acetylcholine at parasympathetic ganglia, in addition to its better known action at the neuromuscular junction. Its effect on the presynaptic vesicles is irreversible, with recovery occurring over a period of three months by re-sprouting of the axons.[4] The effect of external beam radiotherapy in reducing salivary production in patients treated for salivary gland tumors is well recognized.[5] As the mean survival of patients newly diagnosed with ALS is 20–29 months, the risk of inducing cancer in this population is negligible.

This systematic review was conducted to 1) assess the evidence for the effectiveness and toxicity of botulinum for sialorrhea in patients with ALS, and 2) assess the evidence for the effectiveness and toxicity of radiotherapy for sialorrhea in patients with ALS.

Criteria for Selecting Studies for This Review

Experimental and quasi-experimental studies and observational studies, both controlled and uncontrolled, were sought. Single case reports, expert opinions, and studies of retrospective design were excluded. Studies of patients with a diagnosis of ALS and sialorrhea in any health care setting were selected. Studies of patients with sialorrhea as a result of other etiologies were not included.

Reviewed studies included clinical trials of botulinum toxin of any subtype. Trials including any injection technique, frequency of administration, or dose were eligible for inclusion. Eligible trials of radiotherapy could include any modality, dose, or fractionation to salivary glands.

Data were extracted from trials to evaluate efficacy and safety. Specifically, studies were reviewed for the effect of botulinum toxin or radiotherapy on 1) saliva production, 2) quality of life (QOL), and 3) potential adverse effects.

Search Strategy

Databases

The electronic databases Medline (from 1966 to Week 1, April 2006) and Embase (from 1988 to week 15, 2006) were searched via Ovid. The "find similar articles" function was used for all retrieved relevant articles. The final searches of these databases were carried out on April 16, 2006.

From the Cochrane Library (Issue 2, 2006), the Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and the Central Register of Controlled Trials (CENTRAL) were searched via Wiley Interscience. The final search of these databases was carried out on April 17, 2006.

Medline and Embase searches were restricted to studies of humans and publication in English.