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The Management of Oral Secretions in Neurological Disease: A Review

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ABSTRACT

Sialorrhoea is a common and problematic symptom arising from a range of neurological conditions associated with bulbar or facial muscle dysfunction. As well as the physical complications of drooling such as peri-oral chapping, there can be significant embarrassment, which can lead to social isolation and may significantly affect a patient's quality of life. Thicker, tenacious oral and pharyngeal secretions may be a consequence of the drying management approach to sialorrohoea. Co-existence of these types of secretion problems can complicate the management of oral secretions and a balance must be struck to achieve an acceptable outcome.

There are a variety of management approaches for sialorrhoea in neurological diseases, which vary depending on the underlying pathology and severity of symptoms. Interventions include anticholinergic drugs, salivary gland targeted radiotherapy, salivary gland botulinum toxin, and surgical approaches. The management of thick secretions consists of predominantly conservative measures such as using pineapple juice as a lytic agent, cough assist, saline nebulisers and suctioning. These patients may also benefit from mucolytic drugs such as carbocisteine. Currently there is a lack of evidence, and practice varies, but management of sialorrhoea should be part of the multi-disciplinary approach needed for long-term neurological conditions.

WHAT ARE ORAL SECRETIONS?

Problems due to oral secretions are common and can be distressing in a number of neurological conditions. Oral secretion related symptoms can result from saliva, which may vary in consistency from thin and watery to thick and tenacious; but may also be caused by secretions originating in the nose, throat or lungs.[1] The picture is often mixed and a range of treatments are required. For example, muscle weakness in the face leading to poor lip seal may cause problems with drooling but with evaporation from the mouth leading to thickened saliva from the outset. Alternatively thick secretions may occur as a direct result/side effect of the treatments given for managing sialorrhoea. These situations can make management complex, but the aim should be to achieve a balance of symptom control which best improves the quality of life for the patient.

The production of oral secretions

Saliva is produced by six major salivary glands and several hundred minor salivary glands. The major salivary glands are responsible for the production of approximately 90% of the 1.5L of saliva that is produced each day. In healthy individuals the rate of swallowing as a result of pooling saliva is approximately once a minute, although this is variable depending on the rate of salivary production.[2] The submandibular and sublingual salivary glands are primarily responsible for producing background saliva throughout the day, whilst the parotid glands primary function is to secrete saliva during periods of olfactory, gustatory and tactile stimulation.[3] The parotid and submandibular salivary glands are relatively superficial. These differences in salivary gland function may be clinically significant as determining the timing of a patient's saliva problem may allow targeted therapy. Neural stimulation of salivary production is parasympathetic, and contraction of salivary duct smooth muscle is stimulated by the sympathetic nervous system. Stimulation of beta-adrenergic receptors is responsible for the production of mucoid secretions. Oral secretions have several important physiological functions. Saliva protects oral tissue, lubricates food for swallowing and contributes to the maintenance of good dental health. Saliva and mucoid secretions form a vital part of a patient's barrier immune system.[4]

Sialorrhoea and its symptoms

Sialorrhoea is an inconsistently used term most commonly used to describe excessive serous saliva in the mouth which can result from hyper-secretion of saliva, anatomical abnormalities, or facial-bulbar weakness. In neurological conditions the aetiology of this

excessive saliva is weakness or poor coordination of bulbar or facial musculature. This results in ineffective swallowing mechanics, reduced swallowing frequency, poor lip seal and ineffective saliva control, but not excessive production of saliva.[1,5,6] Sialorrhoea commonly affects adults with a variety of neurological conditions including: stroke; neuromuscular diseases such as amyotrophic lateral sclerosis (ALS) / motor neurone disease (MND); and neurodegenerative diseases such as Parkinson's disease (PD), multiple system atrophy, progressive supranuclear palsy, and Lewy Body dementia. Whilst it is often stated that autonomic dysfunction in Parkinson's disease causes hypersalivation contributing to the sialorrhea, studies into salivary production in PD show reduced or normal salivation compared to controls.[5,7]

Estimates of the prevalence of sialorrhoea in those neurological conditions most commonly associated with this symptoms are as follows; PD 10-84%;[5] MND 20- 40%;[8] and cerebral palsy 20%-58%.[9,10]

Physical consequences of sialorrhoea include excoriation of the skin around the mouth, speech and sleep disturbance, dehydration, and increasing fatigue. These physical problems are also associated with psychosocial symptoms such as embarrassment and social withdrawal.[11] In many patients with neurological disease these symptoms will be accentuated by muscle weakness or dystonia in the neck, trunk or limbs causing a flexed posture and/or difficulties maintaining oral hygiene. Saliva may also pool at the back of the throat, causing coughing and a higher risk of aspiration.[12] There are reports of pooling of saliva affecting patient's ability to use non-invasive ventilation (NIV), which in neuromuscular diseases – particularly MND – is an intervention which improves quality of life and survival.[13]

Tenacious saliva and thick secretions

The burden of problematic thickened secretions is also poorly defined. It is important to recognise that patients with sialorrhoea may also have thickened secretions collecting in their mouth and throat, often as a consequence of treatments for sialorrhoea. Thick secretions can lead chewing and swallowing problems and can also impact on the tolerance of NIV.[14,15]

ASSESSMENT OF ORAL SECRETIONS

Areas that are important to clarify include:

1. Evaluating the type of secretions the patient is suffering from i.e. sialorrhoea, thick secretions, or both; consider the impact of saliva collecting at the back of the oral cavity.
2. The cause of the symptoms i.e. does the patient have dysphagia, poor lip seal, learning difficulties, and is there any possibility the patient has anatomical abnormalities or salivary hyper-secretion.
3. The timing of the problem. Whilst unstudied, physiology suggests that if a patient was suffering from symptoms throughout the day, then the targeted therapies such as botulinum toxin and radiotherapy may need to include the submandibular gland, whilst if they had symptoms mainly when eating or drinking, treatment of the parotid glands may be more successful.
4. Whether secretions are impacting on the ability to use non-invasive ventilation.
5. What steps have already been taking to try and manage the problem and what other medication are they on.

Multiple methods of systematically evaluating oral secretions have been used or proposed. Quantitative measures such as weighing cotton rolls and collection cups are largely impractical but can assess reductions in salivary flow. However, such assessments correlate poorly with subjective symptom improvement and so are of little use in clinical practice.[16] There are a number of patient reported and observer reported symptom rating scales. Most of these focus on drooling, but some have proposed including questions assessing other sialorrhoea related symptoms, subjective impact on other aspects of life, and concurrent thick secretion problems.[17,18,19] This lack of an effective or uniform outcome measure for evaluating oral secretion problems is a significant barrier to the generation of good evidence.

MANAGING SIALORRHOEA

A multi-disciplinary approach should be taken; conservative measures such as suction; drug therapy most commonly with anticholinergics; repeated Botulinum toxin injections; radiotherapy and surgical interventions; have all been used to manage sialorrhoea (Table 1). No one treatment modality will be successful for every patient and so a combination of

approaches is required, undertaken in a stepwise fashion (Figure 1).[5,11,20,21] Moreover, patients with different underlying diseases may benefit from different interventions. Notably, sialorrhoea in patients with Parkinson's disease usually occurs during 'off' periods of symptom control. Consequently the most important first step is to optimise dopaminergic therapy to optimise swallowing function.[5]

Table 1: Summary of treatment options

Type of therapy	Benefits of this approach	Side effects	Additional info
Conservative measures	Largely cheap Simple Minimal side effects	Few	Consider these in all patients
Anticholinergics	Easy to prescribe Cheap	Urinary retention, blurred vision, confusion	Caution in myasthenia gravis related drooling
Botulinum Toxin	Targeted therapy	Excessively dry mouth	Concerns over effects on bulbar function
Radiotherapy	Targeted therapy	Excessively dry mouth Risk of malignancy	Effects (including adverse effects) last months to years
Surgery	Long term symptom relief if effective	Generic surgical and anaesthetic risks Retention cysts	Irreversible Patients may be too frail to tolerate

Conservative measures

Although there is little evidence confirming their effect, a variety of conservative measures for managing sialorrhoea and associated symptoms are available. The appropriate use of these conservative managements will vary from patient to patient.

Neck collars and head back wheelchairs are useful devices to improve positioning and counteract a flexed posture. This simple measure is likely to improve patients' comfort and self-image. Speech therapy should be involved at an early stage with the aim to maximise the patients swallowing function and lip seal. Oral prostheses have been trialled in neurologically impaired patients to improve lip seal and have been shown to improve quality of life.[22] For patients with Parkinson's disease, reduced oral sensation or CP, swallow reminders may be of help.[6]

A number of oro-rehabilitation approaches have also been used in neurologically and cognitively impaired children with success. These include oro-motor therapy, biofeedback or behavioural interventions.[23]

Portable suction devices can be considered in patients with treatment resistant symptoms, particularly if they are suffering from pooling of saliva in the throat. Whilst these devices are portable they are not necessarily discrete and patients may find using them embarrassing (Figure 2).

Anticholinergics

Anticholinergics are a group of drugs which inhibit the action of the neurotransmitter acetylcholine at muscarinic receptors, thus reducing saliva production. Care must be taken when using anticholinergics not to cause an excessively dry mouth. This may be more distressing for the patient than their original problem and can contribute to poor oral hygeine.[24,25] There are a variety of anticholinergics and drugs with anticholinergic effects which are used to manage sialorrhoea, including hyoscine hydrobromide, atropine, glycopyrrolate, tropicaimide, hycosamine sulphate and the tricylcic antidepressant amitriptyline (Table 2).[5,20,26] However, evidence supporting these drugs as effective interventions is limited, with only a few studies carried out across a range of diseases. [27]

Table 2: Example anticholinergics used to treat sialorrhoea

Name of Anticholinergic	Preparation	Dose	Specific characteristics and cautions	
Hyoscine Hydrobromide	Trans-dermal patch	0.5mg patch per 72 hours	Associated with a skin reaction at the site of the patch. Frequently altering the patch site and using topically applied steroid may improve tolerance.	[28]
Glycopyrronium	Tablet Oral solution (trialled in children)	1–2 mg 3 times/d	Glycopyrronium has a quaternary ammonium structure which renders it less permeable to the blood brain barrier. Consequently it is likely to be less associated with CNS side effects	[29–33]
Amitriptyline	Tablet	10–50 mg at bedtime	Amitriptyline has a number of other effects which may be exploited. These include sedative and antidepressant effects. However the antidepressant dose is much higher than that typically used to treat sialorrhoea.	[33]
Atropine	0.5% Eye drops	1–2 drops sublingually QDS -6/d	Can be useful if related to meals as it can be administered when the problem occurs.	[34, 35]

Unfortunately, these medications are not specific to the muscarinic receptors of the salivary glands.[25] Patients using these medications for sialorrhoea management are at risk of unwanted effects in other organ tissues. These effects include urinary retention, constipation, increased intra-ocular pressure, cessation of perspiration and increased body temperature and double vision. Moreover, anticholinergics can affect the CNS causing adverse effects such as confusion, disorientation, memory problems, sedation and nausea which can often be intolerable, especially in the elderly.[24,25] The topically applied hyoscine patch can also cause skin irritation which is often severe enough to cause discontinuation.[28]

Parkinson's disease and anticholinergics

It is important to note that there are a set of circumstances relating to Parkinson's disease (PD) that require significant caution when prescribing anticholinergics. Firstly, many patients with PD have autonomic dysfunction and so will be extremely sensitive to the unwanted effects of these drugs on other organs, for example the bladder. Moreover, patients with PD - particularly in its later stages - suffer from cognitive impairment and so may be more likely to become confused when using these drugs. There is also a concern that anticholinergics can cause Tau related pathology and increased Alzheimer's pathology in patients with PD.[36]

Glycopyrronium has a structure which means it does not cross the blood brain barrier; it's use as an oral solution has been trialled in 23 PD patients, showing symptomatic improvement and a good side effect profile.[30] More research is required to determine the appropriateness of anticholinergics in this population and for the reasons outlined above, consideration of botulinum toxin injections at an earlier stage may be appropriate.

Dosing regimes

The optimal doses and delivery mechanisms for these treatments have not been identified, however with a high risk of side effects the approach should be to start at a low dose and titrate up as required and tolerated.

Botulinum toxin

Botulinum toxin is a neurotoxin produced by the bacteria clostridium botulinum. It has been used since the 1980s to treat conditions such as strabismus and dystonia. There are 7 types (A-G) which work by penetrating the axon terminals and degrading SNAP-25 t-SNARE proteins, preventing neuro-secretary vesicles fusion with the nerve synapse plasma

membrane.[37,38] Both Botulinum toxin A and B have been used to manage sialorrhoea (Table 3).[39]

Table 3: A summary of botulinum toxin for the management of sialorrhoea

Toxin Types	Due to multiple Type A botulinum toxin subtypes, direct comparisons between the effects of Type A and Type B toxins are difficult. For the indication of sialorrhoea the comparative dose is approximately Botox® 1: 10 botulinum toxin B.[40]	
	Type A • There are subtypes of Type A botulinum toxin, two of which *(Botox® and Dysport)* are commonly used to treat sialorrhoea. These subtypes have different biological activity, thus dose adjustments must be made accordingly (Botox® 1:3 Dysport).[40]	*Type B (Neurobloc)* • Has a greater propensity for autonomic effects.[40] • Has a higher immunogenicity and so repeated use may have a greater risk of antibody induced failure.[41–43]
Dosing	• Commonly used doses in trials to date 100MU of Botox®; 250MU of Dysport®; 2500MU of Neurobloc. • Doses should be divided between the Submandibular and Parotid glands, with the latter receiving a greater fraction of the total dose. • Optimal therapeutic dose not established. Titrate as appropriate.[44]	
Delivery	*US guidance* • Confirms accurate delivery of the toxin	*Landmark guided* • Practical and largely considered safe *(Figure 3)*
Outcomes of treatment with botulinum toxin	*Benefits* [44] • Meta-analysis data supporting its clinical efficacy • Effective in patients with symptoms resistant to medications • Effects last for 3-6 months • Fewer side effects than anticholinergic medication • Minimally invasive • May decrease risk of aspiration pneumonia in neurologically impaired children.[45]	*Negatives* • Common adverse effects: xerostomia, thickened bronchial secretions and viscous saliva, difficulty chewing and pain at the site of injection. Reverse slowly as toxin effect wears off. [46] • Dysphagia may be a rare side effect.[47] • Repeat injections may result in antibody formation and fading efficacy.[43]
Group characteristics	• MND patients may be more prone to adverse effects and shorter benefit duration compared to the PD patients • Old age may be associated with longer benefit duration.[48]	

Radiotherapy

External beam radiotherapy using photons or electrons is an alternative method for controlling sialorrhoea. It is a treatment modality that is usually employed following the failure to respond to or tolerate treatment with anticholinergic drugs and botulinum toxin. A number of retrospective and prospective studies exist, carried out in patients with PD and MND, reporting objective reductions in saliva production and improvements in subjective patient symptoms.[49] Whilst these studies did not include control groups, the same patients had previously failed to achieve symptomatic control with other available treatments for sialorrhoea. As with botulinum toxin injections, there is no consensus about the optimal dosing regimen for salivary gland irradiation to treat sialorrhoea. Most commonly regimes target both submandibular glands and the caudal two thirds of both parotid glands. Studies to date have used a range of doses, with a median dose per fraction of 5Gy (0.83-8) and a mean total dose of 12Gy (3-48). The length of effect of radiotherapy is variable and was reported to last for several months to 5 years, with around 50% of patients still experiencing effects at 6 months.

Radiotoxicity can occur resulting in an overly dry mouth with more viscous saliva, facial erythema, pain and nausea.[49] These effects are usually short lived and the risk of their development is likely to be reduced with the development of new techniques, such as CT mapping which allows for highly localised therapy [50]**.** Because of the short life expectancy of many of the patients with neurological disease there is less concern about malignancy, however in those with longer life expectancy this may be an unnecessary risk.

Surgical Options

Effective surgical interventions for sialorrhoea do exist. Options include the removal of the submandibular or parotids salivary glands, submandibular and/or parotid duct relocation or ligation, and transtympanic neurectomy.[51] These surgical interventions have most commonly been used in neurologically impaired children with symptoms resistant to medication and botulinum toxin. The use of surgery to manage sialorrhoea in older patients is rare and would only be considered after failure of less invasive approaches.

Meta analysis of surgical options suggests that bilateral submandibular duct rerouting, bilateral submandibular gland SMG excision with bilateral parotid duct rerouting, and bilateral SMG excision with bilateral parotid duct ligation appear to be of similar efficacy.[51] Whilst potentially less effective, four duct ligation offers a simple, quick and safe procedure which may improve symptoms.[52]

Amongst patients with MND, PD and other neuromuscular and neurodegenerative disorders many will not have the functional reserve to tolerate surgical intervention. Additionally, life expectancy is often short and so there is less need for interventions that will work for many years.

MANAGEMENT FOR THICK SECRETIONS

Symptoms related to thickened secretions often are difficult to manage, with the available treatment options more limited than those for sialorrhoea. If a patient is distressed by thickened secretions that are likely to be a result of treatment for sialorrhoea then titrating down to the smallest effective dose can be helpful. Discussions with the patients and carers about which of these opposing secretion problems is more troublesome will help achieve the best balance for the patient.

There are a number of options for alleviating the discomfort associated with thickened saliva, many of which are conservative. Simple approaches include checking the patient's fluid intake, thinning secretions with juices and ice cubes - grape, apple, pineapple or papaya or frequent swabbing of the mouth. The use of a mouthwash of one teaspoon bicarbonate of soda or one teaspoon salt in a glass of water after meals can also be helpful. Mucolytic agents such as N-acetyl cysteine and carbocisteine are effective and commonly used.[53] A pilot study in 1996 investigated the use of beta-blockers in the management of thick mucoid saliva with promising results, but to date there appears not to have been any confirmatory studies.[1]

In patients with more problematic symptoms other measures include nebulised saline to loosen and thin secretions, or using suction pumps and assisted cough techniques to remove secretions.[53]

Key Points

- Sialorrhoea is a common symptom in several neurological conditions. As well as the physical complications of drooling such as peri-oral chapping, there can be significant embarrassment, which can lead to social isolation and affect a patient's quality of life.

- Sialorrhoea can be associated with problems with thicker, tenacious oral secretions. These problems may primarily co-exist with sialorrhoea or may be a consequence of the drying management approach to sialorrhoea. Co-existence of these types of secretion problems complicates the management of sialorrhoea and a balanced approached is needed.

- Sialorrhoea can be managed using a variety of treatments including anticholinergic drugs, salivary gland targeted radiotherapy, salivary gland botulinum toxin, and surgical approaches which should be used in a step-wise fashion.

- Currently there is a lack of evidence directing optimal secretion management but effective long term management is likely to require an MDT approach and a combination of treatments.

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FIGURE LEGEND:

Figure 1: A suggested generic management approach to a patient with symptoms relating to oral secretions. This management approach is derived from expert clinician experience

Figure 2: Portable suction unit

Figure 3: Delivering botulinum toxin Injections by landmark guidance [4]. **Image A – Locating the parotid gland:** Find the mid-point on the line connecting the tragus to the angle of the mandible, approximately the site of the ear lobe. Deliver injection 1cm anterior to this site. **Image B – Locating the submandibular gland:** Find the mid-point between the angle of the mandible and the tip of the chin. Inject 1 finger breadth medial to the inferior surface of the mandible at this point. Direct needle straight upwards, staying as close to the medial surface of the mandible as possible. *NOTE: Adapted from image in 'Srivanitchapoom P, Pandey S, Hallett M. Drooling in Parkinson's disease: a review. Parkinsonism Relat Disord. 2014'*