BRIEF COMMUNICATION

Treatment of the First Bite Syndrome

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KEYWORDS
Parotid; First bite syndrome; Botulinum toxin

Abstract First bite syndrome is a potential complication of surgery involving the infratemporal fossa, deep lobe of the parotid gland and parapharyngeal space. It is described as an acute and intense pain in the parotid region caused with the first bite of each meal. It is related to damage to sympathetic innervation of the parotid gland. Parasympathetic hyperactivation is believed to stimulate an exaggerated myoepithelial cell contraction causing pain. Usual analgesic treatments have poor results. Botulinum toxin type A causes parasympathetic nerve paralysis of the parotid gland and this fact would minimise salivation and decrease first bite syndrome. The aim of this study is to show the details of the technique and our outcomes in 5 patients treated with botulinum toxin type A.

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PALABRAS CLAVE
Parótida; Síndrome del primer mordisco; Toxina botulinica

Tratamiento con toxina botulinica del síndrome del primer mordisco

Resumen El síndrome del primer mordisco es una secuela potencial de la cirugía del espacio infratemporal, lóbulo profundo de parótida y del espacio parafaringeo. Se trata de un dolor agudo e intenso en la región parótidea que se desencadena con el primer mordisco de cada comida. Se relaciona con el daño de las fibras simpáticas que inervan la parótida, lo que resulta en una hipersensibilidad de las células mioepiteliales a la inervación parasimpática, provocando una intensa contracción de las mismas, responsable del dolor causado. No responde a los analgésicos habituales. La inyección de toxina botulinica tipo A en la parótida afectada se presenta...
Introduction

First bite syndrome was described by Haubrich in 1986.\textsuperscript{1} It is a potential sequela of surgery to the infratemporal space, deep lobe of the parotid gland and the parapharyngeal space.\textsuperscript{2,3} It is characterised by acute, sudden facial pain in the parotid region, which often irradiates to the ear and typically occurs at the first bite of each meal. It lasts a few seconds, improves with mastication and is worse at the first meal of the day or after several hours without eating. The symptoms vary from mild to very intense and can even affect quality of life, making eating difficult. Some patients report pain with the salivation that occurs when thinking of food and that the pain is more intense with sialogogue foods (acid).\textsuperscript{2,4}

It is postulated that first bite syndrome occurs due to damage to the fibres responsible for the sympathetic innervation of the parotid gland (sympathetic superior ganglion of the sympathetic cervical chain), specifically its myoepithelial cells.\textsuperscript{2,3} The release of parasympathetic neurotransmitters (acetylcholine) that occurs with salivation and mastication would trigger an intense response in the myoepithelial cells, responsible, in the final instance, for the pain described. Botulinum toxin type A inhibits the release of acetylcholine in the synapses which would lead to a reduction in contraction of the myoepithelial cells and pathological secretion from the glands.

We present 5 patients in this study that experienced this syndrome postoperatively after a parapharyngeal approach and were treated by botulinum toxin type A injection.

Methods

Patients

Five patients were identified who presented first bite syndrome after being operated for a tumour in the parapharyngeal space. They were all treated with botulinum toxin type A injection in the parotid gland. The main characteristics of the patients are summarised in Table 1.

All the patients answered a survey with 4 items (Table 2). Based on a previous study, they were assessed for the presence/absence of symptoms, intensity of pain on the visual analogue scale, the qualitative characteristics of their pain (whether it worsened after time without eating, whether it was worse with sialogogue foods) and whether, if they had known of the existence of this complication, they would have refused or rethought the operation.\textsuperscript{5} The survey was completed prior to the injection, and at one month, 3 months and 6 months after it.

Injection Technique

All the patients were informed of the details of the treatment and the possible side effects and were given an informed consent form. The injection was given between 2 and 17 months after the surgery.

The patients were given a local injection of botulinum toxin type A, reconstituted with 0.9% physiological saline solution. We used insulin syringes (1 ml) for the injection with subcutaneous injection needles (25 G). Each affected parotid gland was injected with 30 U of toxin, distributing the total dose into doses of 10 U injected into different sites of the gland (Fig. 1). The injection was given without local anaesthesia and was well tolerated by all the patients. The details of the dose and injection time for each patient are shown in Table 1. The injection was repeated in 3 patients. Two of them received another 50 U of botulinum toxin type A after six weeks, because their pain had not decreased after the first injection. One case was injected with a further 50 U 7 months after the first injection because their symptoms had worsened.

Figure 1 Botulinum toxin injection sites. It is injected at 1.5 cm from the tragus and is distributed through the parotid region. Although it might be near the facial nerve, botulinum toxin blocks the release of acetylcholine at the level of the neuromuscular plate and therefore the risk of paralysis is low.
Table 1  Characteristics of the Patients and the Injection.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Side</th>
<th>Origin</th>
<th>Histology</th>
<th>Approach</th>
<th>Horner’s syndrome</th>
<th>Sympathetic cervical resection</th>
<th>External carotid ligature</th>
<th>Botulinum toxin units</th>
<th>Repetition of injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>D</td>
<td>Sympathetic nerve</td>
<td>Neurinoma</td>
<td>Transcervical</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>30 U</td>
<td>50 U at 7 months</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>D</td>
<td>Sympathetic nerve</td>
<td>Neurinoma</td>
<td>Transcervical</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>30 U</td>
<td>50 U at 6 weeks</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>I</td>
<td>Carotid</td>
<td>Paraganglioma</td>
<td>Transcervical</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>30 U</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>D</td>
<td>Carotid</td>
<td>Paraganglioma</td>
<td>Transcervical</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>30 U</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>I</td>
<td>Vagus nerve</td>
<td>Paraganglioma</td>
<td>Transcervical</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>30 U</td>
<td>50 U at 6 months</td>
</tr>
</tbody>
</table>

Table 2  Quality of Life Survey.

<table>
<thead>
<tr>
<th>Item</th>
<th>Before injection</th>
<th>One month after injection</th>
<th>Three months after injection</th>
<th>Six months after injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms present</td>
<td>5 (100%)</td>
<td>4 (80%)</td>
<td>4 (80%)</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>Intensity of symptoms (1-10 EVA)</td>
<td>8.5</td>
<td>6</td>
<td>4.6</td>
<td>5</td>
</tr>
<tr>
<td>Type of pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worse with acid</td>
<td>2 (40%)</td>
<td>1 (20%)</td>
<td>1 (20%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Worse after a long time without food</td>
<td>3 (60%)</td>
<td>3 (60%)</td>
<td>3 (60%)</td>
<td>4 (60%)</td>
</tr>
<tr>
<td>Acute, sudden</td>
<td>5 (100%)</td>
<td>5 (100%)</td>
<td>5 (100%)</td>
<td>5 (100%)</td>
</tr>
<tr>
<td>If they had known about this complication, they would have reconsidered their surgery</td>
<td>1 (20%)</td>
<td>1 (20%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

VAS: visual analogue scale.

Results

Three patients’ symptoms were more intense after hours without eating and 2 patients found no association between the intensity of symptoms and the time since the last meal. Likewise, for 2 patients the pain was more intense after salty or acid foods.

The intensity of pain was reduced in 4 patients according to the visual analogue scale (with intensity between 8 and 10) to mild-moderate (with intensity between 2 and 6) at 6 months after the injection, except in one patient whose pain remained severe in intensity. The pain did not completely disappear in any of the patients. One patient acknowledged that had they known of this side effect they would have reconsidered their operation. This patient changed their opinion after the second injection of the toxin and after their pain intensity reduced (Table 2).

None of the patients reported side effects after injection of the toxin.

Discussion

The parotid gland receives dual sympathetic and parasympathetic innervation, which act synergistically and not antagonistically. Electronic microscopy has made it possible to observe how the myoepithelial cells of the gland receive dual innervation (parasympathetic and sympathetic) and both cause contraction of the myoepithelial cells. An absence of sympathetic innervations would result in the hypersensitivity of the myoepithelial cells to...
parasympathetic innervation, and the consequence of this would be ‘‘supramaximal’’ contraction of the myoepithelial cells, which would eventually be responsible for the pain caused on the first bite. Desensitisation occurs after successive bites and the symptoms improve, which then reoccur with the first bite of the next meal. However, this hypothesis has not been proven, since not all patients who have undergone section of the cervical sympathetic chain have this complication. Discovering why some patients develop this and others do not might be the key to establishing the real aetiology of this problem.

First bite syndrome is a minor complication, which often goes unnoticed, but it can interfere with the daily lives of patients and affect their quality of life. Various studies describe first bite syndrome as the most common non-neurological and unexpected complication after surgery to the parapharyngeal space. In a study published by Linkov et al., with 499 patients who had undergone surgical procedures due to tumours (benign and malignant) located in the infratemporal fossa, deep lobe of the parotid gland and parapharyngeal space, first bite syndrome was a complication found in 10% of the patients, with a mean onset time of 97 days after surgery (in our cases the mean onset time was 2 months after surgery). The incidence of this syndrome in our series is lower (7.7% of the parapharyngeal tumours operated in our department between 1980 and 2015) probably because in the first years it was not a routine question in postoperative follow-up checks and, as described in the literature, it can go unnoticed if not taken into consideration.

The factors that are associated with the onset of this syndrome are: injury to the cervical sympathetic chain during surgery, resection of tumours that arise in the cervical chain (2 cases in our series), in the parapharyngeal space, resection of the deep lobe of the parotid gland and manipulation or ligature of the external carotid artery. In 5 of our cases the tumour was located in the parapharyngeal space.

Although the severity of the symptoms tends to diminish over time and they have also been reported to resolve spontaneously, the intensity of the pain necessitates therapeutic intervention of some type. There is no definitive treatment for this complication. Changes to the diet avoiding salogogues and non-steroidal anti-inflammatory drugs have not been shown to be effective. Antiepileptic drugs used in treating neuralgia and neuropathic pain such as gabapentin, gabapentin and carbamazepine have not been demonstrated to be completely effective either. Radiotherapy has been shown to completely resolve symptoms, but it has many side effects and an associated morbidity that does not justify its use for this complication. Surgical resection of the tympanic nerve or the auriculotemporal nerve has also been tried in an attempt to reduce parasympathetic innervations. This has resulted ineffective and invasive.

Injecting botulinum toxin type A into the affected parotid gland is presented as safe and effective in managing this complication. It is an exotoxin with protease activity produced by Clostridium botulinum which blocks the release of acetylcholine in the cholinergic nerve endings. Acetylcholine acts as a neurotransmitter in muscle and gland innervations. Blocking the release of acetylcholine causes a reduction in contraction of the glandular cells and their secretion. Botulinum toxin type A injection has been used safely in routine clinical practice for more than 20 years, and is a useful tool in the head and neck area where it has several applications: to treat facial synkinesis that occurs in facial palsy, to reduce cricopharyngeal spasms, to reduce salivary secretion, and to treat Frey’s syndrome, among others.

There is no protocol for the dose or puncture technique. The dose varies from 10U to 75U and most authors repeat the injection according to how the patients progress. The injection is given without local anaesthesia and is normally distributed diffusely with several pricks into the affected parotid gland. It is occasionally guided by ultrasound.

The indication for botulinum toxin in the treatment of first bite syndrome arose after its efficacy was demonstrated in several studies that raised the hypothesis that reducing or paralysing parasympathetic innervation of the parotid gland would reduce the contraction of the myoepithelial cells, relieving the pain at the start of mastication. Injecting botulinum toxin into the parotid region is a simple procedure that brings about an improvement in symptoms and in the quality of life of these patients, with no side effects of note. Occasionally, after 4–6 months, it will be necessary to repeat the injection, since the effects of botulinum toxin are temporary, until the symptoms resolve.

**Conflict of Interests**

The authors have no conflict of interests to declare.

**References**


**Figure 2** Possible mechanism of action of botulinum toxin type A in first bite syndrome.