Ultrasound-guided botulinum toxin injections for treatment of drooling

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KEYWORDS
Botulinum toxin; Drooling; Sialorrhoea; Salivary glands; Neurological diseases

Summary
Objectives: To evaluate the efficacy of treatment of drooling by ultrasound-guided botulinum toxin injection of the salivary glands and to determine the optimal modalities of this procedure.

Patients and methods: This study is a retrospective review of patients treated for drooling by injection of 100 units of Botox® into the parotid and submaxillary glands between 2002 and 2008. Efficacy was evaluated by a quality of life questionnaire six weeks after the injections.

Results: One hundred and eleven injection sessions were performed in 70 patients aged one to 84 years with a beneficial effect in 66% of cases. The most effective protocol was injection of 20 units of botulinum toxin into each submaxillary gland and 30 units of toxin into each parotid gland.

Conclusion: The treatment of drooling by Botox® injections into salivary glands is effective. The authors propose ultrasound-guided injection of both submaxillary glands and both parotid glands. These injections can be repeated in the case of recurrence of drooling.

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Introduction

Drooling is defined as oral incontinence of saliva secreted in normal quantities and with normal quality [1]. It differs from hypersialorrhoea, which corresponds to increased salivary secretion. This symptom, responsible for psychosocial and physical morbidity, is observed in adults with neurological diseases such as amyotrophic lateral sclerosis, Parkinson’s disease [2,3], sequelae of stroke or brain surgery and head injuries. Drooling is also observed in patients with sequelae of head and neck surgery. In children, drooling is mainly observed in patients with cerebral palsy (33% of patients with cerebral palsy present drooling [4]).

The use of systemic anticholinergic agents [2], atropine and scopolamine, is effective but contraindicated in patients with glaucoma, obstructive uropathy and myasthenia gravis. These treatments, available in the form of scopolamine patches or sublingual atropine drops, have a recognized but limited efficacy due to poor adherence to treatment. Finally, radiotherapy is reserved for elderly patients [5] presenting contraindications to oral treatment or surgery. Surgical treatment by resection of the main salivary glands, ligation or transposition of salivary ducts [6] is proposed after failure of other treatments. Parotid denervation, by tympanic neurotomy via the external auditory meatus, has also been described, but has now been abandoned. Botulinum toxin injection of the submaxil-
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Pharmacologically, botulinum toxin blocks the release of acetylcholine into the neuromuscular synapse, thereby decreasing salivary secretion [8].

This study was designed to evaluate the efficacy of this treatment and to determine the practical modalities of this procedure.

Patients and methods

This retrospective study was conducted on all patients treated by one or several botulinum toxin (Botox®) injection sessions between May 2002 and February 2008. All patients or their legal guardians were informed about the absence of marketing authorisation for botulinum toxin A, Botox® for the treatment of drooling and accepted the principle of this treatment. The patient information specified that Botox® injections were designed to reduce salivary secretion, without completely stopping drooling. Various protocols were applied as a function of the patient and the time at which the injections were performed. The total dose of botulinum toxin injected in every case was 100 mU (mouse units) diluted in 2 mL of physiological saline. The number of injections and the dose injected per gland differed according to the various protocols. The dose in children was 5 mU/kg without exceeding a total dose of 100 mU.

The injection was performed without anaesthesia in adults and under general anaesthesia in children. After disinfection of the skin and the ultrasound transducer (high frequency linear transducer > 7.5 MHz), a sterile ultrasound gel was applied to the skin. The first phase consisted of precise location of the gland to be injected by the radiologist. An Anestago® needle (needles having side-holes) was then introduced perpendicularly to the ultrasound transducer. Botulinum toxin was injected under ultrasound guidance and a second injection, away from the first, was sometimes performed in the same gland. After removing the needle, the salivary gland was massaged to facilitate diffusion of the product.

Efficacy of the injections was evaluated by a systematic telephone interview of the patient or a relative, six to eight weeks after the injection. Questions concerned changes in the number of handkerchiefs used to wipe the patient’s mouth, the need to change clothes, changes in the level of comfort, whether or not another injection would be desired, and the overall efficacy perceived by the patient and the family. A scoring system was based on this clinical interview:

- 0: no efficacy;
- 1: partial efficacy (persistence of minimal drooling, partial improvement of quality of life, insufficient improvement in relation to the patient’s expectations);
- 2: good efficacy but of brief duration (< 1 month);
- 3: very effective: resolution of drooling and the discomfort experienced by the patient;
- 4: unknown (patient died or lost to follow-up).

Results

Seventy patients between the ages of one and 84 years (29 females and 41 males) were included. A total of 111 injection sessions were performed, as some patients were treated several times. The diseases most frequently associated with drooling were amyotrophic lateral sclerosis (ALS), Parkinson’s disease and cerebral palsy. Causes of cerebral palsy, other than neonatal causes, were Rett syndrome, epileptic encephalopathy and brain tumours. Patients treated for surgical sequelae had been operated by total pharyngolaryngectomy in two cases, supracricoid laryngectomy in two cases and supraglottic laryngectomy in one case. Most patients received a single injection session (65%) and 24% of patients received a second injection session. These data are summarized in Table 1.

Table 2 presents the distribution of the 100 units of botulinum toxin between the various salivary glands according to the various injection protocols. Seven protocols were used, comprising variable numbers of injection sites and variable doses in each parotid and submaxillary gland.

No efficacy was observed in 25.4% of cases (score 0). Partial efficacy was observed in 22.5% of cases (score 1), brief efficacy was observed in 1.8% of cases (score 2) and very good efficacy was observed in 42.3% of cases (score 3). Nineteen injections could not be evaluated (patient lost to follow-up, dead or impossible evaluation). Good and partial efficacy of injections according to the protocol used and the underlying disease is presented in Table 3. A second injection session was performed in 38 patients, with good efficacy in 51.8% of cases and partial efficacy in 22.2% of cases. No major complication was observed (haematoma of the floor of the mouth or paralysis).

Comparison of these results with published literature, derived from all 19 studies based on more than 10 patients conducted between 1997 to 2007, is presented in Table 4.

Discussion

Botulinum toxin injection of the salivary glands to reduce drooling is widely indicated in certain neurological diseases [9–11]. A review of the indications in the various published studies shows that botulinum toxin is mainly used in children with cerebral palsy (30%), patients with Parkinson’s disease (20%) and patients with amyotrophic lateral sclerosis (15%) [12]. There is a general consensus concerning the efficacy of this treatment in these diseases [12] and this treatment was effective in 66.6% of cases in the present study.

In more than half of the published studies, only the parotid glands were injected, while only the submaxillary glands were injected in 9.5% of studies and both glands were injected in 38% of studies. The submaxillary gland is the main gland responsible for resting saliva secretion, while the parotid gland is predominantly active during mastication [13]. We therefore propose systematic injection of all four glands in order to reduce permanent drooling and drooling during meals.

Twenty of the 41 studies published in the literature were performed with ultrasound guidance, while the other authors used anatomical detection of the gland based on palpation. Only one study compared these two methods: Dogu et al. [14] showed that ultrasound guidance provided better results. In agreement with this author, we consider that systematic ultrasound guidance of injections is essential, as it provides good visualization of the injection site and
diffusion of the toxin in the gland, thereby avoiding accidental injection into adjacent muscles, which constitutes a rare but serious complication of treatment. No serious adverse effects were observed in the present series. The only minor adverse effects were swollen glands following the injection, thicker saliva and mainly pain during injection. Many authors use lidocaine cream for local anaesthesia in adults and general anaesthesia in children to avoid the pain of injection. In the present series, all children under the age of 15 years were treated under general anaesthesia, but local anaesthesia did not appear to be useful in adults, as pain is due to injection of the gland rather than skin effraction.

In this series, botulinum toxin injections were considered to be very effective in 42.3% of cases and partially effective in 22.5% of cases. The efficacy of the various injection protocols could not be compared statistically due to the heterogeneous populations in each group. Published series are also based on relatively small sample sizes, preventing statistical comparison of the various injection protocols. However, in the present series, based on a large sample size (70 patients), the results of botulinum toxin injections can be analysed quantitatively according to the disease responsible for drooling and according to the injection protocol used.

Protocol 6 (only one injection of 25 mU per gland) was preferred in children with small salivary glands to avoid any risk of injection beyond the gland. This protocol was effective in 77.7% of cases. With this protocol, the volumes injected were proportionally greater than those used in adults, due to the smaller size of the salivary glands, suggesting that the use of a larger volume of the same concentration in adults could possibly improve the efficacy of these injections.
In 10 patients with various chronic neurological diseases, including four patients with ALS, Porta et al. [15] reported an efficacy of botulinum toxin injections for four to seven months. The present series comprised a large number of patients with ALS (n = 25), in whom only protocol 2 was effective in 68.7% of cases. Pal et al. [16] reported an efficacy of 66% for botulinum toxin injections in nine patients with Parkinson’s disease, while, in the present series, protocol 2 was effective in 77% of patients with this disease (13% partial efficacy and 64% good efficacy).

Protocol 2 was the protocol most frequently used in this study, based on the efficacy of the other protocols and published data. This protocol was most effective in Parkinson’s disease, but the global efficacy (partial and good) remained relatively constant regardless of the disease responsible for drooling, ranging from 68.7% to 100%. This protocol, which consists of a single injection of 20 mU into each submaxillary gland and two injections of 15 mU into each parotid gland, was the most effective of the seven protocols used in this study, with an efficacy of 72%. In line with Jongerius et al. [17], it therefore appears legitimate to perform a single injection of a relatively large dose into the submaxillary glands and two injections into the parotid gland.

The loss of efficacy of botulinum toxin at the synapse, to which it is permanently bound, is due to axon regrowth. This phenomenon partly explains recurrence of drooling symptoms some time after treatment, which may require another injection session. Among the patients treated by several injection sessions (n = 38 patients), efficacy appeared to globally increase with the number of injections.

Evaluation of the efficacy of botulinum toxin injection cannot be based on objective parameters, as an objective reduction of saliva flow rate is not necessarily correlated with improvement of drooling and patient comfort. The methods of objective quantification show poor reproducibility from one patient to another and do not

### Table 4 Published studies conducted between 1997 and 2007, including more than 10 patients.

<table>
<thead>
<tr>
<th>Authors</th>
<th>n/disease</th>
<th>Guidance</th>
<th>Evaluation</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogu 2004 [15]</td>
<td>15/Parkinson</td>
<td>Ultrasound vs anatomical</td>
<td>Cotton rolls</td>
<td>4.4 months</td>
</tr>
<tr>
<td>Ellies 2004 [18]</td>
<td>33/varied</td>
<td>Ultrasound</td>
<td>Sialometry</td>
<td>3 to 7 months</td>
</tr>
<tr>
<td>Ellies 2003 [13]</td>
<td>13/varied</td>
<td>Ultrasound</td>
<td>Clinical Salivary ultrasound</td>
<td>4 to 7 months</td>
</tr>
<tr>
<td>Friedman 2001 [19]</td>
<td>11/Parkinson</td>
<td>Anatomical</td>
<td>Cotton rolls</td>
<td>6 months</td>
</tr>
<tr>
<td>Jongerius 2004 [4,17]</td>
<td>45/Cerebral palsy</td>
<td>Ultrasound</td>
<td>VAS, DQ</td>
<td>6 months</td>
</tr>
<tr>
<td>Lipp 2003 [20]</td>
<td>30/varied</td>
<td>Anatomical</td>
<td>Cotton rolls</td>
<td>1 to 6 months</td>
</tr>
<tr>
<td>Mancini 2003 [21]</td>
<td>20/Parkinson</td>
<td>Ultrasound</td>
<td>DRS Questionnaire</td>
<td>1 months</td>
</tr>
<tr>
<td>Marks 2001 [22]</td>
<td>28/Parkinson</td>
<td>Anatomical</td>
<td>VAS, DQ Questionnaire</td>
<td>1 to 5 months</td>
</tr>
<tr>
<td>Nobrega 2007 [23]</td>
<td>21/Parkinson</td>
<td>Ultrasound</td>
<td>DRS</td>
<td>3 to 5 months</td>
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<tr>
<td>Ondo 2004 [24]</td>
<td>16/Parkinson</td>
<td>Anatomical</td>
<td>DRS</td>
<td>3 to 5 months</td>
</tr>
<tr>
<td>Porta 2001 [15]</td>
<td>10/varied</td>
<td>Ultrasound</td>
<td>VAS</td>
<td>4 to 7 months</td>
</tr>
<tr>
<td>Savarese 2004 [25]</td>
<td>23/Cerebral palsy</td>
<td>Anatomical</td>
<td>VAS</td>
<td>2 months</td>
</tr>
<tr>
<td>Suskind 2002 [26]</td>
<td>17/Cerebral palsy</td>
<td>Ultrasound</td>
<td>Cotton rolls</td>
<td>1 to 8 months</td>
</tr>
<tr>
<td>Wan 2005 [27]</td>
<td>58/varied</td>
<td>Ultrasound</td>
<td>DRS</td>
<td>2 months</td>
</tr>
<tr>
<td>Kalf 2007 [3]</td>
<td>17/Parkinson</td>
<td>Ultrasound</td>
<td>DRS</td>
<td>3 months</td>
</tr>
<tr>
<td>Gerlinger 2007 [28]</td>
<td>21/Cerebral palsy</td>
<td>Ultrasound</td>
<td>Cotton rolls</td>
<td>1 to 6 months</td>
</tr>
<tr>
<td>Verma 2006 [29]</td>
<td>10/ALS</td>
<td>VAS</td>
<td>Questionnaire</td>
<td>3 months</td>
</tr>
<tr>
<td>Su 2006 [30]</td>
<td>15/Parkinson</td>
<td>Cotton rolls</td>
<td>DRS</td>
<td>4 months</td>
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DQ: drooling quotient; DRS: drooling severity and frequency.
take into account circadian fluctuations of saliva flow rate. It therefore appears preferable to use simple, subjective methods, based on clinical interview of the patient or the patient’s family. In this series, all patients were asked, six to eight weeks after treatment, about their overall satisfaction and their desire to repeat injection sessions and not about a possible reduction of the saliva flow rate.

However, a marked disparity of efficacy was observed and it is difficult to quantitatively evaluate the patient’s global impression that ranged from complete satisfaction to total inefficacy of injections, despite the use of a standard protocol. No reliable explanation can be proposed for this phenomenon, which probably has a multifactorial origin, including a placebo effect on the postural disorders and disorders of deglutition responsible for drooling, which are not modified by reduction of saliva flow rate.

Conclusion

Drooling is a common symptom associated with neurodegenerative diseases, cerebral palsy and many diseases causing postural disorders and disorders of deglutition. The present series, comprising 70 patients, is the largest series since the introduction of botulinum toxin injections for the treatment of drooling. It clearly demonstrates the efficacy of these injections on the patient’s quality of life, making botulinum toxin injection the treatment of choice for drooling. The various studies published in the literature are difficult to compare in view of the very variable doses, injection techniques and diseases treated. This study has the advantage of using various injection protocols in a large number of patients with various diseases to determine the most effective injection sites and doses. In this study, the efficacy on quality of life appeared to be dependent on the dose injected into the submaxillary gland and was independent of the characteristics of parotid gland injections. We therefore propose two injections of 15 mU into each parotid gland and one injection of 20 mU into each submaxillary gland with ultrasound guidance.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


