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Can we justify the continued use of botulinum toxin A in the management of myofascial pain?

Abstract

We initially performed a pilot study to evaluate the impact of botulinum toxin A (BtA) on increased masseteric mass with associated pain. We assessed the impact on the muscle mass and the impact, if any, on each patient's reported pain before and after injection in a group of 10 patients who were refractory to conservative management methods. Results of this pilot study indicated that clenched and unclenched muscle dimensions showed no statistically significant reduction (-0.82 clenched and -1mm unclenched). However, what did prove to be significant was an improvement in their pain scores as measured on a Visual Analogue Scale (VAS). Pre-injection mean VAS score was 8.2 and 1.8 at 6 weeks post-injection. Following the pilot study we focused just on patients' pain scores. Our main study included 48 patients (81 muscles) who suffered with pain secondary to increased masseteric size whom indicated their pain score out of 10 on the VAS prior to placement of BtA in to each affected masseter muscle, and a further pain-score recording 6 weeks post-injection. Results showed a mean pre-injection pain score of 7.9 and a mean post-injection pain score of 2.9. Our trust has allowed funding to provide the intramuscular injection of BtA in appropriately selected patients following the results of this study on reported pain alone, which has justified its continued use.

Introduction

Masseteric hypertrophy is a condition that presents as a unilateral or bilateral swelling in the region of the angle of the mandible (1). Increased muscle mass can also be caused by myospasm linked to myofascial pain and dysfunction (MPD) or in fact a combination of the two (2). The aetiology is unclear but might include increased work muscle mass due to parafunctional habits e.g. chewing gum, bruxism or changes in proprioceptive influences (3,4). This increase in muscle volume has been linked to temporomandibular joint disorder, focal dystonia and the premature loss of teeth (3, 4).

Diagnosis is achieved by simple clinical examination but investigations such as plain view radiography, computed tomography, magnetic resonance scanning and ultrasound scanning (1,3,4,5) can be helpful. Muscle biopsy has also been described (1) and this or direct surgical view of the affected muscle is usually the only way of definitively diagnosing between hypertrophy and myospasm. Patients can complain of the cosmetic appearance of the enlargement of the masseter muscle (3) which can be accompanied by trismus and pain (3,6,7) impacting on daily activities e.g. eating and talking.

Treatment of increased masseteric mass with associated pain and functional impairment can involve the excision of part of the masseter muscle by an intra-oral and/or an extra-oral approach (1-4) or removal of part of the mandibular ramus (6,7). These options are invasive and can lead to significant post-operative morbidity. A less invasive option includes the injection of botulinum toxin A (BtA) in to the masseter muscle (1-7). We have been using the technique for several years in our unit, although little evidence on its reduction in pain, impact on quality of life (QoL) or muscle mass is present in the available literature.

The cost of BtA is not insignificant and with the growing importance of patient reported outcome measures in the provision of healthcare, within the current financial climate, it is important to ascertain that a treatment modality is effective and how just how much information is needed to support this.

Our aim was to determine whether patients find BtA beneficial in the management of increase in masseteric mass with accompanying pain. In a pilot study we performed pre- and post- injection ultrasonography and recorded any impact on muscle mass plus reported pain scores in the same group of patients, and then continued on to a further study of simply looking at myofascial pain pre- and post- injection.

Patients and Methods

Pilot study

A pilot study included 10 patients, all of which had a degree of unilateral or bilateral masseteric hypertrophy/ enlargement and complained of pain plus patient perceived difficulty in mouth opening. 3 patients had unilateral pain and 7 had bilateral pain.

Patients included in the study had previously undertaken a 3 month period of jaw exercises following assessment by a specialist physiotherapist in the hospital. They had also been advised on daily warm compresses, massage and taking regular analgesia/ non-steroidal anti-inflammatory medication during this time period. Parafunctional habits were identified and excluded. If any

bruxists were identified a lower soft acrylic 2mm mouthguard was prescribed by their dentists and worn nightly. At 3-month review, if the patient reported little or no improvement in pain and they remained to have clear masseteric enlargement on clinical examination, they were then recruited in to the study. Hypertrophy and pain reporting was not measured prior to 3 months of conservative management. No exclusions were made over age or gender, all patients were classed as grade I or II by the American Society of Anaesthesiologists' physical classification system. No patients were rejected after the study began.

Suitable patients were recruited consecutively after assessment by the same Consultant Oral and Maxillofacial Surgeon. Directly prior to recruitment they had temporomandibular joint open and closed mouth plain radiographs to assess movement and formation of the mandibular condyle to exclude pathology. If they did they were excluded from the study and further imaging and appropriate treatment offered. Exclusion was also made if they had previously had the injection of BtA in to their masseter muscle/s or any previous temporomandibular joint surgery. No patients recruited had an MRI scan. No patients were rejected after the start of the pilot study.

Prior to intervention with BtA measurements were taken of affected masseter muscles using ultrasonography. The machine used was LOGIC™ P9 (GE Healthcare). Measurements were taken with each patient at rest and also whilst clenching at the maximum distance form superficial to deep aspects of the masseter at 90 degrees to the skin surface. Each patient had ultrasound scanning by the same Consultant radiologist within 4 weeks prior to, and at 6 weeks post, injection of BtA. Measurements were taken at the maximum thickness of the muscle.

All patients were administered the intra-muscular injection of BtA by the same consultant oral and maxillofacial surgeon. The drug used for injection was Allergan (Allergan Limited, The Parkway,

Marlow, England). Each 50unit vial of Allergan (Botox ®) was diluted with normal saline to a concentration of 25 units/mL. Each muscle received the injection of 25 units/mL. At administration the muscle was palpated and BtA injected in to the thickest, or most hypertrophied, part of the muscle. Injection was with a fine 25-gauge needle after aspiration to avoid intravenous placement.

Patients were asked to record their pain associated with their masseter muscles on a visual analogue scale (VAS) (Figure 1) on a scale of 1-10, with 10 being the worst pain imaginable, just before the administration of BtA and also 6 weeks later at review on the same day as their post-injection ultrasound scan. These were retained in the patient's hospital notes.

Pre- and post-treatment VAS scores were compared using a paired T test. Pre- and post- treatment muscle dimensions were compared using a fixed gradient, random intercept linear mixed model in order to account for clustering of left and right sided muscle dimensions by patient. All statistical analyses were done using IBM SPSS Statistics version 25 (2017).

Main study

Following from the results of the pilot study, we then extended our study to only record the VAS scores of all patients included. 48 patients were included (81 muscles). Recruitment and inclusion criteria remained the same, enlargement/ hypertrophy of the masseter was assessed and identified clinically and confirmed with ultrasonography. Methodology was largely the same with 3 main changes from the pilot study; all muscles received an intra-muscular injection of 50 units/mL, no patient received a post-operative ultrasound scan and VAS was recorded pre-injection and 6 weeks post-injection, as in the pilot study, but for each muscle as opposed to per patient. No patients were rejected from the main study after recruitment. Patients were reviewed at 6 months post-injection of BtA.

After discussion with our local institutional research and development review board an exception from the requirement of ethical approval was granted for this prospective study and it was accepted as a service evaluation project.

Results

Pilot study:

10 patients participated and completed the pilot service evaluation, requiring treatment to a total of 17 muscles.

Results 1: Difference in masseteric mass pre- and post- intramuscular injection of BtA in pilot study

All patients showed little to moderate improvement in ultrasound guided measurement of masseter muscle mass (Table 1). Pre-treatment clenched muscles had a mean size of 14.12mm (range 10-19). Post-treatment clenched muscles had a mean size of 13.29mm (range 8-18). The mean change in clenched muscle size was -0.82 mm (95% CI -1.96:0.315), *p* 0.16. Pre-treatment unclenched muscles had a mean size of 12.00 mm (range 8-16). Post-treatment unclenched muscled had a mean size of 11.00 mm (range 8-15). The mean change in unclenched muscle size was -1mm (95% CI -1.90:-0.098), *p* 0.030.

Results 2: Change in VAS score pre- and post- intramuscular injection of BtA in pilot study

Pre-treatment mean VAS score was 8.2 (95% CI 7.38-9.01). Post-treatment mean VAS score was 1.8 (95% CI 0.85-2.74) with a mean VAS score difference of 6.4 before and after treatment (p value for difference < 0.01). All patients showed an improvement of reported pain before and after BtA injection recorded per patient (Figure 2).

Main study:

48 patients participated and completed the main service evaluation study, requiring treatment to a total of 81 muscles.

Results 3: Change in VAS score pre- and post- intramuscular injection of BtA for each muscle in main study

Pre-treatment mean VAS score was 7.94 (95% CI 7.70-8.18). Post-treatment mean VAS score was 2.86 (95% CI 2.56-3.17) with a mean VAS score reduction of 5.08 before and after treatment (p value for difference < 0.05). All patients again showed an improvement in pain score before and after BtA injection per muscle recorded (Figure 3).

Results 4: 6 month follow up main study patients

Of 48 patients 9 (14 muscles) had moved out of area or were lost to follow up, 29 patients (49 muscles) attended with improved symptoms and requested no further follow up and 10 patients (18 muscles) attended saying that the improvement they had found from the BtA injection had diminished over time and requested further injection. No one requested a different treatment modality.

Discussion

Botulinum toxin A (BtA) has been in clinical use for a number of indications for many years. It is effective in the management of many different clinical problems including the management of Frey's syndrome (8), drooling (9), recurrent temporomandibular joint dislocation (10) and to assist wound healing (11). BtA is a potent neurotoxin produced by Clostridium botulinum (4).

BtA's mode of action is to block the release of acetylcholine into the synaptic cleft which suspends neuromuscular transmission. When injected into a muscle it reduces muscular activity (10) and in turn it produces muscle paralysis, weakness and atrophy (4). This should occur between days 2-20, but often regresses at 2 - 4 months when new terminal axons form to restore the neuromuscular transmission (3) and muscle paralysis starts to recover (12,13), hence why we reviewed our patients at 6 weeks post-injection. We routinely use it in our department for treatment of increased masseteric mass accompanied by pain, however in recent years due to its cost we have found its use increasingly scrutinised.

The main concern of some patients with increased masseteric size in previously published studies are related to cosmetic appearance (1,4,5,6). So far Sidebottom et al are the only authors in the available literature to look at functional impairment, namely restriction in mouth opening (2). In our pilot and main studies all patients had an increase in masseteric muscle mass accompanied by pain and patient perceived difficulty in mouth opening. Pain within enlarged muscles is usually caused when a trigger point or points develop. These contraction knots within the muscle are accompanied by sensitised nociceptors both with a sensory and motor element (2,14).

There is an growing importance to show a measured improvement in any pathological process or in a patient's pain, and hence quality of life (QoL), following a specified treatment. The importance of patient reported outcome measures (PROMS) has come to the forefront in the commissioning of healthcare services in the UK in recent years (15,16,17).

The value of PROMS has become increasingly examined as part of service quality evaluation in research and audit. Traditional outcome measures, such as muscle mass reduction in this study,

are now being matched by PROMS in terms of importance in service provision. For this reason it is now becoming more pertinent to show that a particular treatment or intervention is successful in both aspects (15,16).

QoL, specifically health related QoL, is defined as a patient's perception of the impact of their disease, or treatment of the disease, on their daily life and their physical, psychological and emotional wellbeing related to it (18,19). Recording a simple VAS score is a quick and easy way to report a patient's overall health related QoL before and after treatment.

In contrast to the clear difference in patient reported pain we were unable to show clear evidence for a difference in muscle dimension before and after treatment in our pilot study. Our best estimate is that clenched muscle dimension decreased by around 0.8 mm, and unclenched muscle dimensions decreased by 1.0mm, but the statistical evidence for this was equivocal (*p* value 0.16 and 0.030, respectively). One potential explanation is that this service evaluation lacked statistical power to identify small to medium sized changes in muscle size. Alternatively, it is possible that there is little change in muscle mass at the low doses of BtA used in this service evaluation, which are lower than those reported elsewhere in the literature (3,4). Another possibility is the prospect that instead of hypertrophy these patients were suffering with myofascial pain and dysfunction from myospasm and this could be why no significant difference was seen.

This service evaluation was conducted to explore patient perception and experience of treatment using BtA for masseteric enlargement and differs from a clinical trial. All patients knew they were receiving the injection of BtA in the aim to improve their QoL by improving their pain scores, and this may have motivated patients to report an improved VAS score than they had actually

experienced. There was no control group so we cannot distinguish between the effects treatment on pain scoring and the effect of time.

VAS scoring was also not reported anonymously therefore patients may have felt pressure to report an improvement, or more of an improvement, than they did in fact experience. VAS scores were recorded on separate sheets of paper therefore the patient would not have been reminded of their initial score, so they could have been less tempted to simply record lower for their second score.

VAS scores may be seen as a crude demonstration of QoL and seen as too simple. We could have used a longer questionnaire, for example the EQ-3D-3L, to include more specific, generic QoL questions to give a better picture of their perception of their overall QoL on that day. We have used the EQ-3D-3L previously in our department with success in the reporting of QoL after mandibular third molar extraction (19,20). We felt the VAS reporting gave us the information we required, without the need for a more-lengthy questionnaire.

Similarly, the ultrasound scanning estimates of muscle dimension in the pilot study are imperfect and do not gain any information on the medio-lateral dimension. The exact point of reference within the muscle can differ at separate appointments. However, we felt this method was appropriate because it is non-invasive, safe and provided the information that we required in this study. It has also been used with success in previous studies in the area. We did not find feel it appropriate to perform a more validated scanning method to assess muscle dimension e.g. computed tomography or magnetic resonance imaging.

This service evaluation provides valuable insight into the impact that masseteric hypertrophy can have on patients. This could lead on to further studies in to QoL related to BtA treatment of hypertrophy. As authors, we would recommend running full clinics of patients requiring BtA injection to improve productivity, and reduce wastage of BtA, particularly with single muscles being injected. Once the vial of BtA powder is opened and mixed with saline it must be used, or any remaining disposed of immediately.

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Figure legend:

Figure 1 : Visual Analogue Scale (VAS) data collection form used to report overall QoL related to their pain associated with masseteric hypertrophy

Figure 2 : Trend in VAS difference for each patient demonstrating overall QoL change pre- and post- intramuscular BtA injection pilot study

Figure 3 : Trend in VAS difference for each patient demonstrating overall QoL change pre- and post- intramuscular BtA injection main study

Table 1 : Masseter muscle mass as demonstrated by ultrasonography pre- and post- intramuscular BtA injection pilot study