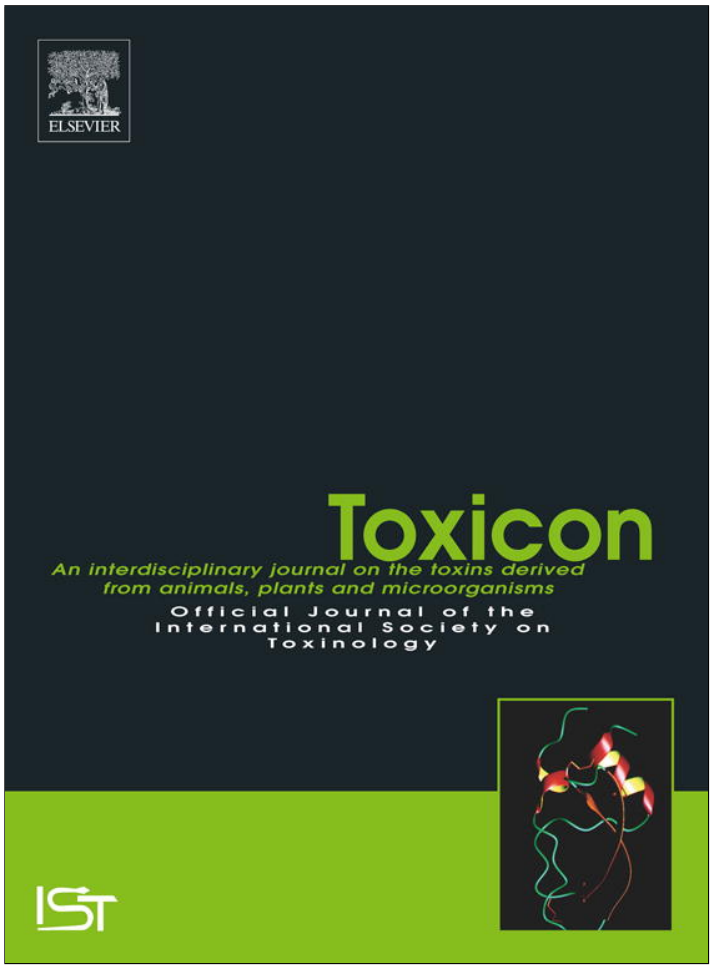

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Improvement in pelvic pain with botulinum toxin type A – Single vs. repeat injections

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ABSTRACT

The aim of this prospective study was to report the outcomes of pain and vaginal pressures of successive botulinum toxin type A injections for women with objective pelvic floor muscle overactivity and a two-year history of pelvic pain. Between 2005 and 2008, 37 women underwent injection of 100 IU of botulinum toxin type A into the puborectalis and pubococcygeous muscles with dysmenorrhoea, dyspareunia, dyschesia, and non-menstrual pelvic pain assessed using a visual analogue scale (VAS), and vaginal pressure measured by vaginal manometry, at 0, 4, 12 and 26 weeks from each injection. 26 women (70%) had one injection of botulinum toxin type A and 11 (30%) had 2 or more injections. The second injection was performed at the earliest at 26 weeks after the first, with subsequent injections having a median time to re-injection of 33.4 weeks (range 9.4–122.7 weeks). Single and repeated injections both demonstrated a statistically significant reduction in dyspareunia by VAS scores from 54 to 30 in the single injection group and from 51 to 23 in the multiple injection group ($p = .001$), non-menstrual pelvic pain VAS from 37 to 25 ($p = .04$), as well as vaginal pressures; 40 versus 34 cm H_2O ($p = .02$). No statistically significant difference in dysmenorrhoea or dyschesia was observed for either group from their baseline scores. Multiple injections of botulinum toxin type A in women with pelvic floor muscle overactivity provide significant relief from dyspareunia and non-menstrual pelvic pain. The upper limit between re-injection is not yet determined, nor is the maximum number of treatments. Clinical outcomes for single and subsequent injection of botulinum toxin type A for recurrent pelvic pain are equivalent. Women who have had benefit from a single injection of botulinum toxin type A can be reassured that if symptoms reoccur, repeated injections can be expected to be equally efficacious.

1. Introduction

Botulinum toxin type A produces localised muscle weakness or paralysis through biochemical denervation and is used for the treatment of many neuromuscular disorders, as well as chronic pelvic pain and pelvic floor overactivity (Jankovic and Brin, 1991; Maria et al., 2000; Abbott, 2009; Bjornson et al., 2007). Reduction in pain is associated with a return to normal physical activity, mood and quality of life (Stones et al., 2000). Clinical effects are often seen within 1 week of injection, and benefits typically last from 3 to 6 months. Multiple dosing is utilised to extend the treatment effect and has been demonstrated to be beneficial in neuromuscular disorders, muscle spasticity and detrusor overactivity (Bakheit et al., 2001).

There are limited data on the long-term effects of recurrent dosing with botulinum toxin type A, however there is concern with regards to potential toxicity, antibody

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formation and secondary failure of botulinum toxin type A treatment (Lange et al., 2009). Given the proximity of pelvic sphincters to the injection site for gynaecological applications of botulinum toxin type A, the effects of long-term muscle wasting and remodelling on both target- and non-target muscles is critical in the evaluation of this treatment (Fortuna et al., 2011).

Our unit has previously conducted a series of studies demonstrating that the use of botulinum toxin type A improved pelvic pain and vaginal pressures in women with pelvic floor muscle hypertonicity (Abbott et al., 2006; Jarvis et al., 2004). This study aims to report the longitudinal outcomes for repeat injections of botulinum toxin type A into the pelvic floor muscles of women with objective pelvic floor muscle overactivity, as well as the interval to re-injection, pain outcomes and vaginal pressures with repeated injections.

2. Materials and methods

This is a prospective cohort study carried out at the Department of Endo-Gynaecology, Royal Hospital for Women, Sydney, Australia. This study received approval from the institutional scientific and ethics committees (HREC ref 03/102).

2.1. Eligibility

Between August 2005 and December 2008, women aged between 18 and 55 years with a minimum two-year history of pelvic pain and who had previously completed either the pilot study or the randomised controlled trial (RCT) were invited to participate. Eligibility criteria included documented pelvic floor overactivity with at least two of the following: pelvic floor myalgia on palpation; vaginal manometry reading of greater than 40 cm H_2O; or chronic pelvic pain. Willingness to attend follow-up and compliance with the study protocol were essential. Study participants were consented following the receipt of written information and the opportunity to ask research staff study-related questions.

2.2. Exclusion criteria

Exclusion criteria included: current pregnancy or desire for pregnancy in the six months following injection; inability to tolerate vaginal pelvic floor muscle examination and manometry; breast feeding; or those not willing to use a reliable method of contraception. Women with a known contraindication for the use of botulinum toxin type A, those with history of neuromuscular and/or bleeding disorders were excluded, as well as those who were using aminoglycoside antibiotics or had poor comprehension of written and spoken English.

2.3. Data collection

Participating women were asked to complete demographic data and underwent full medical history and detailed examination. Assessment of pain was performed by visual analogue scale (VAS) with separate scores obtained for dysmenorrhoea, dyspareunia, dyschesia, and non-menstrual pelvic pain. Pelvic floor pressure was measured by vaginal manometry via an air-filled vaginal probe (Peritron; Cardio Design, Melbourne, Australia). Recorded assessments included resting pressure and maximum contraction pressure.

2.4. Botulinum toxin A injection procedure

The injection procedure has been previously described (Jarvis et al., 2004) and is summarised here. Under conscious sedation monitored by an anaesthetist, the pelvic floor muscles were examined vaginally and 100 IU of botulinum toxin type A (BOTOX, Allergan Westport, Ireland) diluted in 4 ml of normal saline was injected into two sites bilaterally within each of the puborectalis and pubococcygeous muscles in divided doses. Women recovered for 1–2 h until they could eat, drink, mobilise, and void. Initial follow-up was by telephone call 2–3 days after injection, and post-procedure reviews were performed at 4, 12 and 26 weeks from each injection. At each follow-up, study participants completed VAS scores for pain and were examined to assess pelvic floor tenderness and record vaginal manometry.

2.5. Patient groups

Women in the single injection group came from the placebo group of patients in the RCT and were botulinum toxin type A naïve. During the study period, these women may not have received a second injection due to complete resolution of symptoms; no improvement with the first dose of botulinum toxin type A; or desire not to continue with further dosing. This group was used as the comparator for the multiple injection group. After injection, routine follow-up was not extended beyond 26 weeks.

Repeat injections of botulinum toxin type A were offered to women who had a good clinical response to the index injection with changes in pain symptomatology. Recurrence of pelvic pain and clinical signs of pelvic floor myalgia on palpation determined the timing of re-injection. Women who had repeat injections followed the same protocol used for the initial injection and returned for timed follow-up to assess the effect of each subsequent injection.

2.6. VAS scores

Changes in VAS scores for pain and vaginal pressures were assessed in each of the single and multiple injection groups over the follow-up period. A comparison between the single and repeat injection groups was also made to determine if repeated botulinum toxin type A dosing continues to be effective.

2.7. Statistical analysis

Statistical analyses were performed using SPSS 20.0 (SPSS Inc, Chicago, IL). The Kolgarov–Smirnov test was performed to determine the distribution of data. Baseline to 26 week post-treatment data was compared using the Freidman test for multiple dependent non-parametric data.

Probability values are two-tailed, with a significance set at $p < .05$. The Mann Whitney *U* test was used to compare data from the single and multiple injection groups. Comparisons of VAS from baseline to each follow-up were analysed using Wilcoxon's signed-rank test.

3. Results

3.1. Demographics

Thirty-seven women, aged 21–52 years were recruited to the study. The demography and history of the participants requiring single injection and multiple injections were similar and are outlined in Table 1. There were 66 distinct injections of botulinum toxin type A administered to 37 women over the study period. Twenty-six women (70%) had one injection of botulinum toxin type A and 11 (30%) had two or more injections. The median number of repeat injections was 3 (range 2–6). Median time to re-injection for responders was 33.4 weeks (range of 9–123 weeks).

3.2. Pain VAS scores

The VAS scores for pain symptoms are shown in Table 2. Dyspareunia and non-menstrual pelvic pain were significantly reduced following botulinum toxin type A administration in both the single and repeat injection groups. Non-menstrual pelvic pain was not significantly reduced in either group at 4 weeks post-injection, however, by the 12 and 26 week follow-up there was a significant reduction in VAS score for both groups. In the single injection group, the VAS was reduced from 45 at baseline to 15 at 12 weeks ($p = .001$) and to 20 at 26 weeks ($p = <.001$); in the multiple injection group, there was a corresponding reduction from 37 to 12 ($p = .005$), and 37 to 25 ($p = .008$) respectively. The maximal reduction of VAS scores for dyspareunia was at 4 and 12 weeks for the multiple and single injection groups, respectively, and for non-menstrual pelvic pain at week 12 in both groups. There was no significant difference from baseline in dysmenorrhoea or dyschesia following botulinum toxin type A in either the single or multiple injection groups.

Median baseline scores for dysmenorrhoea were significantly reduced in the multiple injection group when compared to single injections (42 vs. 64; $p = .016$). There were no other significant differences between the groups over the follow-up period.

Table 1
BMI, body mass index. Data are displayed as median (interquartile range) or *n* (%) unless otherwise specified. Data were compared using Mann–Whitney *U* test for continuous data or Pearson chi-square for categorical data.

	Single injection ($n = 26$)	Multiple injection ($n = 11$)	*p*
Age (y)	30 (26–41)	31 (26–42)	.64
BMI (kg/m^2)	24 (22–29)	23 (21–26)	.82
Smoker-current	7 (27%)	2 (18%)	.48
Regular exercise	16 (62%)	3 (27%)	.06
Parous	9 (35%)	4 (36%)	.71

Table 2
VAS, visual analogue scale. Data are median (interquartile range) unless otherwise specified.

Week	Single injections		Multiple injections		p^a
	VAS	p^b	VAS	p^b	
Non-menstrual pelvic pain					
0	45 (25–51)		37 (25–57)		.60
4	38 (7–52)	.06	21 (5–45)	.08	.48
12	15 (0–47)	.001	12 (4–29)	.005	.96
26	20 (0–36)	<.001	25 (0–47)	.008	.70
Dysmenorrhoea					
0	64 (36–72)		42 (34–50)		.016
4	57 (11–72)	.42	10 (0–19)	.49	.40
12	52 (19–72)	.70	31 (12–49)	.19	.17
26	52 (22–64)	.20	50 (29–70)	.46	.37
Dyspareunia					
0	54 (12–76)		51 (42–65)		.74
4	33 (5–70)	.041	20 (2–44)	.008	.28
12	25 (0–54)	.031	23 (0–51)	.012	.84
26	30 (5–46)	.002	23 (0–40)	.021	.42
Dyschesia					
0	12 (0–46)		0 (0–35)		.41
4	0 (0–42)	.18	0 (0–33)	.57	.69
12	0 (0–52)	.56	4 (0–25)	1.00	.76
26	0 (0–44)	.24	10 (0–41)	.69	.95

[a] Data for the two groups were compared using Mann Whitney *U* test.
[b] Data represent change in VAS from baseline to 4, 12 and 26 weeks respectively and were compared using Wilcoxon's signed-rank test.

3.3. Vaginal pressure

Fig. 1 summarises the comparison of resting and maximum vaginal pressure throughout the study. Median resting pelvic floor manometry at baseline was 47 cm H_2O (range: 38–54 cm H_2O) in the single injection group and 40 cm H_2O (range 35–51 cm H_2O) in the repeat injection group. A significant reduction in resting pressure was demonstrated in both the single ($p < .001$) and multiple injection ($p = .014$) groups over the course of the follow-up. In addition, there was a significant reduction in maximum contraction pressure in both groups at the 4 and 12 week follow-up visits. This difference did not persist at the 26 week follow-up in either group.

The multiple injection group recorded lower maximum contraction pressures than the single injection group at baseline (35 vs. 10 cm H_2O, $p = .002$), 4 weeks (20 vs. 7 cm H_2O, $p = .001$) and 12 weeks (25 vs. 5 cm H_2O, $p = <.001$ respectively) suggesting a residual baseline muscle effect in the recurrent dose group.

3.4. Adverse effects

There were no major adverse effects following any of the individual botulinum toxin type A injections. In 23/66 (35%) injections cold-like symptoms were reported within the 26-week follow-up period. One woman reported vulval irritation post injection following her first injection. There was no reported urinary or faecal incontinence following any botulinum toxin type A injection.

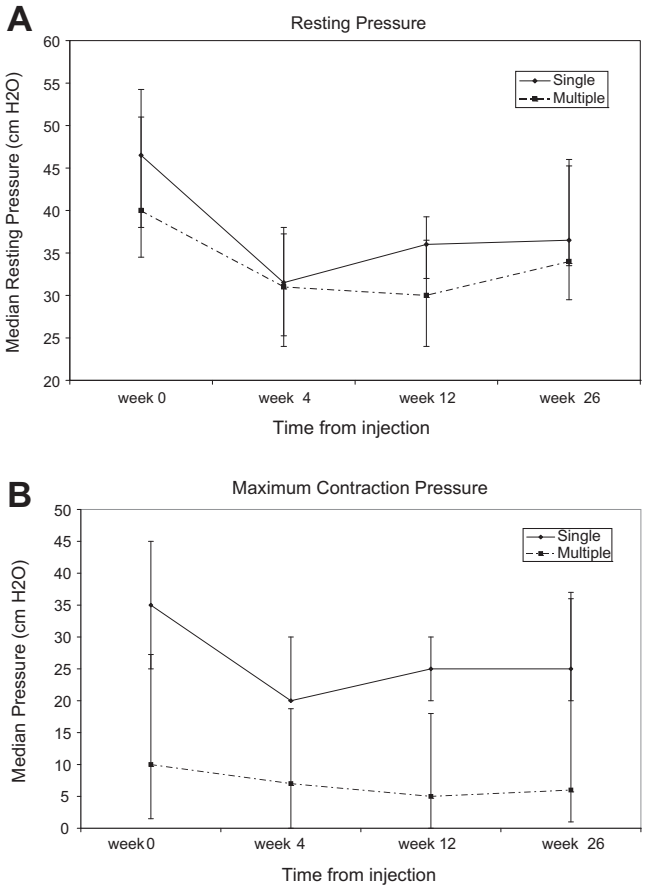

Fig. 1. A. Resting pressure. **B**. Maximum contraction pressure (increase above resting pressure). Horizontal lines represent median scores, and vertical lines represent interquartile range.

4. Discussion

4.1. Single vs. repeat injections

Following failure of conservative treatment for chronic pain, botulinum toxin type A has been successfully used (Abbott, 2009; Abbott et al., 2006; Jarvis et al., 2004; Thomson et al., 2005), however there are few long-term clinical results available. Repeat injections are described for muscle overactivity including stroke patients and cerebral palsy (Bjornson et al., 2007; Bakheit et al., 2001), cervical dystonia causing migraine (Truong et al., 2008; Blumenfeld et al., 2003; Binder et al., 2002) and detrusor overactivity (Sahai et al., 2007).

In this study, data suggest that botulinum toxin type A naïve women responded just as those in our previous studies (Abbott et al., 2006; Jarvis et al., 2004), with reduction in objective vaginal pressure, dyspareunia and non-menstrual pelvic pain. Indeed, with the combination of participants from the RCT and the pilot data, a significant reduction was demonstrated at 12 weeks follow up for non-menstrual pelvic pain which was not seen in the RCT. This reflects the larger cohort with greater power. Dysmenorrhoea is not affected by botulinum toxin type A in keeping with previous work demonstrating dysmenorrhoea is common in women even in the absence of pathology (Abbott et al., 2002). The significant difference at baseline for dysmenorrhoea between single and multiple injection groups may reflect a cumulative effect of treatment, however more likely the small sample size and non-randomised nature of the study are factors.

Pain symptoms are again reduced with subsequent injections of botulinum toxin type A to the pelvic floor muscles without substantial side effects – an important point when counselling women with an initial good result about outcomes for repeat injections. At subsequent injection, there does appear to be a cumulative effect with lower vaginal pressures and a lower maximal contraction pressure. For both single and multiple injection groups, there is a slow but sustained increase vaginal pressure over 6-months although this pressure does not always correlate with pain recurrence.

At 33 weeks, the median time for repeat injection is longer than the 12–26 weeks cited for activity of botulinum toxin type A (Smaldone et al., 2010; Simpson et al., 2008). This time frame reflects the fact that women will return for review outside a clinical study only with increased pain, not due to increased vaginal pressure, whereas other applications of botulinum toxin A require re-injection for muscle overactivity prior to the advent of pain. A possible contributor to this prolonged clinical effect may include the fact that botulinum toxin type A may have local analgesic and anti-inflammatory properties, although this remains controversial (Sycha et al., 2006). Another explanation for the difference in timing of botulinum toxin A re-injection between the pelvic floor and muscles of movement may rest in the limited nature of the function of the pelvic floor muscles, with no antagonist musculature. All patients were regularly reviewed by a physiotherapist as part of their treatment with botulinum toxin A. Compliance with physiotherapy treatment may have also been a factor in increasing the length of time to re-injection, however this was not measured in our study.

For women requesting repeat injection, the clinical findings were a more important determinant compared to time. This did lead to the earliest subsequent injection occurring at 9 weeks and whilst neutralising antibody formation (see 4.2) may have been a factor, the most likely reason for this early re-injection is that the target muscles were missed.

We acknowledge that the self-selection of women in the repeat injection group who had previously had a good response could bias a comparison of pain scores – however this is the objective of the current study and indeed we observed a range of pain response in both initial and repeat injection groups.

4.2. Neutralising antibodies

Long-term treatment with botulinum toxin type A is generally well tolerated and effective, however after an initial positive therapeutic effect symptoms may fail to respond to subsequent treatments (Dressler, 2002). Secondary non-response has been attributed to the development of neutralising antibodies to botulinum toxin type A, although this correlation has not shown to be strong and other factors including disease progression are implicated

(Lange et al., 2009). The presence of neutralising antibodies were more likely for conditions requiring doses of botulinum toxin type A >6000 Ipsen Units and re-injection intervals <3 months. In our study, botulinum toxin type A is given in 100 Allergan Units doses at intervals usually longer than 3 months, meaning the development of antibodies is an unlikely contributor to secondary non-response for this indication and other investigations and treatments for pelvic pain should be considered when this occurs.

4.3. Architectural changes

Muscle fibre wasting and reduced contractility is seen in both target and non-target muscles following repeated injection of botulinum toxin type A, in rabbits (Fortuna et al., 2011). Such architectural changes will reduce symptoms from pelvic floor overactivity, but may also contribute to longer-term issues such as pelvic sphincter failure and pelvic organ prolapse. Urinary and faecal incontinence are reported to be temporary following botulinum toxin type A to the pelvic floor muscles (Abbott et al., 2006), however there is little known about the longer-term implications, especially with repeat dosing. Data from this study demonstrates reduced resting pressures of the pelvic floor muscles following botulinum toxin type A, as well as lower contraction pressures in the multiple injection group, which may indicate early atrophic changes. Whilst hypothetical only at this time, further studies are required to determine structural changes in addition to relevant clinical changes.

4.4. Side effects

The side effects reported in this study were not considered serious and importantly, in light of the above discussion of possible architectural change, there was no failure of pelvic sphincter function for women in the short term. Long-term data would however be valuable.

5. Conclusion

In conclusion, botulinum toxin type A is an effective treatment for pelvic floor muscle overactivity, in both single and multiple dosing regimes. Long-term side effects seen in other non-gynaecological studies of repeat botulinum toxin type A injections seem to be associated with higher dosing and shorter treatment intervals making toxicity and the development of antibodies unlikely for current gynaecological indications. Local muscle effects of remodelling and atrophy could be of some concern given the proximity of sphincter muscles to the site of pelvic floor muscle botulinum toxin type A injection. Ongoing long-term follow-up studies to monitor for any of these issues are required.

Women may be reassured that multiple injections of botulinum toxin A are equally effective as the initial injection if required for recurrence of symptoms.

Conflict of interest

None.

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