OnabotulinumtoxinA (Botox) Nerve Blocks Provide Durable Pain Relief for Men with Chronic Scrotal Pain: A Pilot Open-Label Trial

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ABSTRACT

Introduction. Chronic scrotal pain (CSP) is a common, often debilitating, condition affecting approximately 4.75% of men. While nerve blocks using local anesthetics usually provide temporary pain relief, there are no publications on the use of longer acting nerve blocks to provide more durable pain relief for men with CSP.

Aim. The aim of this study was to determine if onabotulinumtoxinA (Botox) cord blocks provide durable pain relief for men with CSP.

Methods. In this pilot open-label study, men with CSP who had failed medical management but experienced temporary pain relief from a standard cord block underwent a cord block with 100U Botox.

Main Outcome Measures. The outcomes measured were changes 1, 3, and 6 months post-Botox injection in (i) a 10-point visual analog scale (VAS) pain score; (ii) scrotal tenderness on a three-point scale as rated by physical examination; and (iii) the Chronic Epididymitis Symptom Index (CESI) to measure the severity and impact of scrotal pain on men. Paired t-tests were used to compare groups.

Results. Eighteen patients with CSP seen between April and September 2013 had Botox injected as a cord block. At the 1-month follow-up, pain reduction was reported by 72% of patients (mean VAS score: 7.36 vs. 5.61, \( P < 0.003 \)), while by physical examination 44 and 34% of the men had either complete or partial resolution of scrotal tenderness. In addition, there was also a significant reduction in CESI scores (22.19 vs. 19.25, \( P < 0.04 \)). At 3 months, 56% had both sustained pain reduction and reduced tenderness based on the VAS score (mean: 7.36 vs. 6.02, \( P < 0.05 \)) and physical exam. The CESI score continued to be significantly lower. Unfortunately, by 6 months, most men had a return to their baseline levels of pain and tenderness.

Conclusions. Our pilot study found that Botox cord blocks provide pain reduction for 3 months or more for most men with CSP. Khambati A, Lau S, Gordon A, and Jarvi KA. OnabotulinumtoxinA (Botox) nerve blocks provide durable pain relief for men with chronic scrotal pain: A pilot open-label trial. J Sex Med **;**:**–**.

Key Words. Botox; Chronic Scrotal Pain; OnabotulinumtoxinA

Introduction

Chronic orchialgia or chronic scrotal pain (CSP) is defined as “intermittent or constant unilateral or bilateral testicular pain three months or longer in duration that significantly interferes with daily activities” [1]. This is a common condition and many will have severe disabling pain for months or years with disruption of their normal lives. CSP can be caused by various processes including infectious (epididymitis, prostatitis), benign (hydrocele, spermatocele, varicocele), testicular malignancy, postsurgical (vasectomy, hernia repair, scrotal procedure), radiculopathy, neuropathic, or referred pain [2]. Hence, a thorough history and physical examination is essential in order to characterize, locate, and treat the underlying source of pain [3]. Unfortunately, almost 25%
of cases remain idiopathic and the therapies are often empiric [1]. Patients are usually treated in a step-wise fashion, with medical management involving antibiotics, anti-inflammatories, and analgesics being the first steps. Next course of therapy includes regional nerve blocks using a combination of local anesthetic and/or steroids, with or without ultrasound guidance [4]. Invasive options include microsurgical denervation of the spermatic cord, which is shown to be effective in up to 96% [5–7] of cases and with a 75% success rate at 20 months of follow-up [8]. Finally, epididymectomy or orchiectomy has been performed with variable success rates. Costabile et al. demonstrated that the clinical benefit of orchiectomy is uncertain, as 80% of patients continued to experience significant pain [9].

The finding of nerve blocks providing short-term relief of scrotal pain coupled with the effectiveness of denervation of the spermatic cord in reducing or eliminating scrotal pain prompted us to consider the use of a longer acting nerve blocking agent. OnabotulinumtoxinA (Botox: Allergan, Irvine, CA, USA) provides temporary but long-acting sensory fiber nerve blocks [10,11]. OnabotulinumtoxinA has been used by urologists for the treatment of painful pelvic and bladder disorders, overactive bladder syndromes, and benign prostatic hypertrophy [12,13]. In this study, we administered Botox cord blocks to assess its effectiveness in providing durable pain relief for men with non-neuropathic scrotal pain.

**Aim**

The aim of this study was to determine if the use of Botox as a cord block provides durable pain relief for men with CSP.

**Methods**

After approval from our research ethics board, 18 patients with CSP seen between April and September 2013 were enrolled in our study. Exclusion criteria included men trying to conceive with their partners in the next 6 months, history of allergic reaction to Botox and human serum albumin, history of motor neuron disease or neurogenic bladder, use of anticoagulation or blood dyscrasias, and inability to provide informed consent. They underwent a comprehensive workup with a thorough medical and psychiatric history, physical examination, and investigations including Doppler ultrasonography of the scrotum, urine, and semen studies. No specific reversible cause was identified for the pain. All patients failed conservative management with anti-inflammatories, antibiotics, anticonvulsants, and analgesics, but experienced temporary pain relief felt to be significant by the patients from a spermatic cord block using a 10 cc solution of 0.5% Marcaine (Hospira, Montreal, Quebec, Canada) and 2% xylocaine. These patients were offered a cord block with Botox. The possible benefits of longer term relief but also the risk of complete failure, hypersensitivity reactions, generalized muscle weakness, and sensory changes were explained. After consent was obtained, we proceeded with the Botox injection. One hundred units of Botox was reconstituted in 10 cc of normal saline, and injected into the upper scrotum approximately 1–2 cm distal to the external ring, infiltrating the branches of the genitofemoral and the ilioinguinal nerves, identical to the technique described by Issa et al. [14] This technique is similar to the cord block widely used by urologists, with extra care being taken to confirm with each injection that the injection is not into any vascular structure. Before injection, the syringe is aspirated to confirm that the needle is not entering an artery or vein. All blocks were administered by the same person (K.A. Jarvi).

**Main Outcome Measures**

The objective measures to document changes in pain were changes following the Botox cord block in a visual analog pain score and the Chronic Epididymitis Symptom Index (CESI). The subjective measures were changes in tenderness of the scrotum by physical examination. Patients were asked to fill a 10-point visual analog pain scale (VAS) before Botox injection and, 1-month, 3-month, and 6-month following injection. In addition, they were also subjected to careful physical examination of the scrotum with their tenderness in the testis and epididymis rated on a zero- to three-point scale (this is a nonvalidated scale used at our center to grade tenderness; 0 being no tenderness and 3 being exquisitely tender) and sensory changes noted at each visit. This provided another means of assessing the degree of scrotal tenderness in patients. All physical exams were performed by the same individual (K.A. Jarvi). Finally, patients also completed the CESI at each visit. Paired t-test was used to analyze the VAS score, physical tenderness rating, and CESI score before and after administration of Botox cord block.
Results

The mean age of the patients and the duration of CSP were 44 years and 4.4 years, respectively. All patients had unilateral CSP. Physical examination revealed epididymal tenderness in all patients, with no person having testicular tenderness as the only site of scrotal tenderness. Ten patients had other regional chronic pain syndromes, with five having pain in the ipsilateral conjoint tendon, three having pain at the level of the ipsilateral external ring, and two having inguinal pain above the external ring. Etiology was vasectomy in six patients, idiopathic in five, hernia repair in three, and trauma and infection in two.

At the 1-month follow-up after Botox, as measured by the VAS score, 13 (72%) patients experienced improvement in their score from baseline (mean: 7.36 vs. 5.61, \( P < 0.003 \)) (Table 1). It should be noted that 10/18 of the men had chronic regional pain syndromes in addition to the CSP, so they continued to experience pain in the region even if the pain in the scrotum resolved. In addition, by physical examination; complete resolution of tenderness in the epididymis was noted in 8 (44%) patients, with a reduction in scrotal tenderness overall in 14 (78%). There was no change in the degree of tenderness in four (22%) patients. The mean reduction in tenderness was by 1.27 points (\( P < 0.0001 \)). There was also a significant difference in the mean CESI scores from baseline to 1-month follow-up after Botox (22.19 vs. 19.25, \( P < 0.003 \)).

One patient underwent orchiectomy prior to the 3-month follow-up visit. At 3 months, 10 (56%) patients had lower VAS scores (mean in the group: 7.20 vs. 6.02, \( P < 0.05 \)) with 5 (28%) patients having no scrotal tenderness by physical examination. Based on our three-point tenderness scale, a reduction in tenderness on physical examination was observed in 10 (56%) patients, with a mean reduction of 1.04 points (\( P < 0.003 \)). There continued to be a significant difference in the mean CESI scores (22.19 vs. 19.67, \( P < 0.044 \)).

Prior to the 6-month follow-up visit, four patients underwent a repeat Botox injection for a recurrence of the scrotal pain. The mean time to the second injection was 152 days. In addition, five patients underwent an alternative surgical procedure (microsurgical denervation \( \times 4 \), vasovasostomy \( \times 1 \)). Hence, only eight patients had no interventions prior to the 6-month assessment. The mean VAS score, tenderness score, and CESI score was 6.2, 1.2, and 19.8, respectively, at 6 months in these eight men. Overall, the effectiveness of the Botox cord block declined at 6 months, with only 22% noting an improvement in their VAS and CESI scores.

We also studied eight patients with isolated scrotal pain in the absence of other regional pain. In this group, six patients (75%) experienced a significant improvement in their VAS scores at 1 month (7.69 vs. 5.00, \( P < 0.002 \)) and 3 months (5.92, \( P < 0.03 \)). By physical examination, seven patients (87%) had reduced tenderness and four of eight patients (50%) had no tenderness 1 month following injection. There was a significant reduction in the mean tenderness score by 1.38 points (\( P < 0.0001 \)) and 1.08 points (\( P < 0.003 \)) at 1 month and 3 months, respectively. Similarly, six of eight patients (75%) experienced an improvement in their CESI scores at 1 month (21.61 vs. 18.5,

### Table 1  Effect of Botox on VAS scores, tenderness score on physical exam, and CESI scores on follow-up visits

<table>
<thead>
<tr>
<th></th>
<th>Baseline (pre-Botox)</th>
<th>1-month F/U</th>
<th>3-month F/U</th>
<th>6-month F/U</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS score (10-point scale)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean VAS score</td>
<td>7.36 (( P &lt; 0.003 ))</td>
<td>6.02 (( P &lt; 0.05 ))</td>
<td>6.2 (( P &lt; 0.1 ))</td>
<td>8</td>
</tr>
<tr>
<td>% improved pain</td>
<td>72% (13/18)</td>
<td>56% (10/18)</td>
<td>22% (4/18)</td>
<td></td>
</tr>
<tr>
<td>Tenderness score (0–3 scale)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean tenderness score</td>
<td>2.13 (( P &lt; 0.0001 ))</td>
<td>1.09 (( P &lt; 0.003 ))</td>
<td>1.2 (( P &lt; 0.01 ))</td>
<td>8</td>
</tr>
<tr>
<td>% improved pain</td>
<td>78% (14/18)</td>
<td>56% (10/18)</td>
<td>28% (5/18)</td>
<td></td>
</tr>
<tr>
<td>Partial</td>
<td>34% (6/18)</td>
<td>28% (5/18)</td>
<td>28% (5/18)</td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>44% (8/18)</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CESI score</td>
<td>22.19</td>
<td>19.25 (( P &lt; 0.04 ))</td>
<td>19.67 (( P &lt; 0.05 ))</td>
<td>19.8 (( P &lt; 0.3 ))</td>
</tr>
<tr>
<td>% improved score</td>
<td>72% (13/18)</td>
<td>50% (9/18)</td>
<td>22% (4/18)</td>
<td></td>
</tr>
</tbody>
</table>

*All \( P \) values compared with baseline

CESI = Chronic Epididymitis Symptom Index; F/U = follow-up; VAS = visual analog scale
P < 0.05). However, there was a nonsignificant difference at the 3-month (P < 0.07) mark.

Lastly, we performed unpaired t-test of the differences in the VAS, physical tenderness, and CESI scores at 1 month between patients with regional pain disorders and patients with scrotal pain only before and after Botox administration. There was no significant difference in the mean reduction of VAS scores, physical tenderness scores, or CESI scores between the two groups.

There were no complications involving bleeding, pain at injection site, or muscle weakness. Three patients experienced transient scrotal/inguinal paresthesia; however, this resolved in all cases by 3 months.

Comment

Pain is caused by activation of peripheral nociceptors by noxious stimuli. These signals are then transmitted via type-A delta and type-C fibers through neurotransmitters such as substance P to the central nervous system. In the pathologic state of chronic pain, sensitization of neurons and neural plasticity leads to abnormal, sustained activation of nociceptors to even innocuous stimuli [15]. Chronic pain is a common condition, affecting 16–29% of the population in various developed countries [16–18].

OnabotulinumtoxinA has been used by physicians to treat chronic pain syndromes, most frequently for the management of migraine headaches [10,19]. OnabotulinumtoxinA belongs to the family of clostridial neurotoxins. It acts at the neuromuscular junction and induces muscle relaxation by inhibiting the release of acetylcholine from the presynaptic neuron. However, neuroregeneration by axonal sprouting limits the duration of its effects to a few months [10,11]. Botox also has an analgesic effect and has been extensively investigated in the management of headaches and migraine. The mechanism by which it exerts this effect is not entirely clear, but appears to be mediated by a reduction in the release of neurotransmitters involved in pain such as substance P, calcitonin gene-related peptide, and glutamate [20,21]. Two large multicenter randomized placebo controlled trials—Phase III Research Evaluating Migraine Prophylaxis Therapy 1 and 2—used a total dose of 155 to 195U of Botox. The Botox arm experienced a significant improvement in quality of life measures and a decrease in the duration and frequency of headaches compared with placebo [22,23].

Botox has been reported to be useful as a treatment for urological pain syndromes such as interstitial cystitis and pelvic pain [12,13]. We extended the application of Botox to another chronic pain condition, CSP, which can adversely impact the physical, social, psychological, and economic well-being of an individual. The prevalence of scrotal pain is estimated to be 4.75%, and this is expected to rise with increased awareness [24]. Empiric therapy generally involves antibiotics, anti-inflammatories, analgesics, and neuropathic agents. Refractory cases are offered nerve blocks and surgical therapy is reserved for patients who fail all these measures.

Orchiectomy has been performed for CSP with variable success, with Davis et al. reporting a success rate of 73% with the inguinal approach in a series involving 15 testicles treated [1]. Similarly, Yamamoto et al. reported a success rate of 75%, but the study only involved 4U [25]. This should be considered as the last option because of the potential adverse effects on the individual's endocrine and fertility potential. Moreover, Costabile et al. demonstrated that the clinical benefit of orchiectomy is uncertain, as 80% of patients continued to experience significant pain [9].

Epididymectomy was reported to be effective in patients with postvasectomy pain, with 93.3% experiencing improvement during a mean follow-up of 7.4 years [26]. However, Sweeney et al. found that only 32% experienced resolution of symptoms after this procedure [27]. On the other hand, multiple series have investigated the role of microsurgical denervation of the spermatic cord in CSP, with up to 96% of men experiencing complete pain relief [5–7]. The long-term success rates are lower, with just over 70% experiencing relief at 20 months of follow-up [8].

Unfortunately, there is no minimally invasive form of treatment that can potentially provide long-term pain relief in patients with CSP. While orchiectomy can negatively influence the psychological well-being of an individual, it also leads to the loss of vital endocrine function. On the other hand, epididymal surgery can contribute to infertility due to obstruction in a relatively young population. Even though denervation provides a testicle-sparing option, this still requires a general anesthetic. Moreover, long-term complications such as testicular atrophy, wound infection, and fluid collections including hydrocele and seroma have been reported [8]. Basal et al. published the successful use of pulsed radiofrequency denervation of the spermatic cord in patients with idio-
pathic CSP [28]; however, this was a small case series of five patients, which will require a larger study to establish its role in management of these patients.

We report a prospective pilot study on the first use of Botox for spermatic cord block in patients who failed all conservative measures for treatment of CSP. We chose to inject Botox 100U because we wanted to have very low risks of complications, and this dose was lower than the 155–195U reported to be used, with limited complications, for the treatment of migraines and headaches. This was administered as a simple, quick, and minimally invasive outpatient procedure in patients who had experienced short-term pain relief with a standard cord block. It is important to note that 56% of our patients had another chronic pain condition (pain in the inguinal canal, conjoint tendon tenderness, and external ring tenderness), which made these a very complex group of men to study.

Following the Botox injection, 72% had improvement in their VAS score. The change in the VAS score was small (6.02 after vs. 7.2 before Botox), but the VAS score was a global measure of pain in the groin, so the men who had a combination of scrotal and inguinal pain (56% of the men) tended to have little or no reduction in the VAS score for pain, even if the scrotal pain was completely gone. A number of these men also had inguinal pain, which was not the target of this Botox block and understandably still complained of pain in the inguinal region after the block. Additionally, 78% had reduced scrotal tenderness based on their physical examination at 1 month, with 44% being completely free of tenderness in the scrotum. At the 3-month follow-up, 56% continued to experience reduced pain as measured by the VAS score. By 6 months, most of the patients either required a repeat Botox injection or pursued an alternative surgical therapy.

Patients were also asked to complete their CESI questionnaire. This is a validated symptom index developed by Nickel that assesses scrotal pain and its impact on quality of life in patients with chronic epididymitis [29]. The average CESI score in their patients with chronic epididymitis was 13.8, much lower than the average score of 22.19 in our patients with CSP, indicating that our men had significantly more symptoms and impact than the patients in the Nickel series [29]. There was a significant improvement of almost three points (to 19.25) in the mean CESI score after Botox at 1 month. However, clinically, it is unclear what a three-point difference would mean on an individual basis. There was durable improvement in pain and quality of life at 3 months; however, this was not significant at the final 6-month visit.

Overall, it is important to recognize that this is a complex population often with pain in the inguinal region in addition to the scrotum. Even though Botox cord block can reduce scrotal tenderness, the perceived pain reduction as measured by the VAS scores may not decline to such an extent because of the frequent finding of concomitant pain arising from the inguinal canal or the conjoint tendon.

This is the first study using Botox to treat men with CSP. While the results are promising, it must be remembered that this was a pilot study and a larger study is required to confirm these results and to understand the clinical significance of the use of Botox. In addition, close to 30% of men with chronic pain respond to a placebo therapy [29], so a randomized, placebo controlled study is required to better assess the efficacy of this novel treatment for CSP.

Conclusion

This is the first report of the use of Botox to treat men with CSP. The majority of the men experienced reduced pain for at least 3 months following the Botox injections, with 44% having no scrotal tenderness, but most of them had a return to baseline levels of pain and tenderness by 6 months. This is the first report of the use of Botox to treat men with CSP and indicates that Botox has the potential to be used as a minimally invasive procedure to treat men with CSP. Larger studies are needed to confirm these findings and to establish the role of Botox in the clinical management of men with CSP.

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Statement of Authorship

Category 1

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(c) Analysis and Interpretation of Data
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(b) Revising It for Intellectual Content
Allan Gordon

Category 3

(a) Final Approval of the Completed Article
Aziz Khambati; Susan Lau; Allan Gordon; Keith A. Jarvi

References


