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Mini Review

Nonsurgical Management of Chronic Exertional Compartment Syndrome with Botulinum Toxin-A

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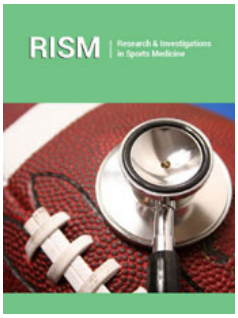
ISSN: 2577-1914



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Submission: February 14, 2022

Published: March 16, 2022

Volume 8 - Issue 3

How to cite this article: Cage SA, Galbraith RM, Trail LE, Peebles RL, Cox C, Warner BJ. Nonsurgical Management of Chronic Exertional Compartment Syndrome with Botulinum Toxin-A. Res Inves Sports Med. 8(3), RISM.000688. 2022. DOI: 10.31031/RISM.2022.08.000688

Abstract

Chronic Exertional Compartment Syndrome (CECS) is a potentially disabling condition that can cause lower leg pain, increased intramuscular pressure, decreased strength, and other neurological symptoms. Current conservative treatment options fail at a high rate, leading to individuals discontinuing their current level of activity, or electing for surgical fascial release. However, even with surgical fascial release, CECS patients experience a relatively high recurrence of symptoms. One non-surgical treatment method has been the use of botulinum toxin-A injections into the affected lower leg compartments. Based off the available literature, botulinum toxin-a appears to reduce pain and intramuscular pressure in CECS patients. While there are potential adverse effects to the use of botulinum toxin-a, these can often be mitigated using proper dosing and approved botulinum toxin-A preparations. More research is needed to fully understand the mechanism how botulinum toxin-a improves CECS symptoms. In the interim, with proper usage, patient education and communication, botulinum toxin-A has the potential to be a safe and effective treatment option for CECS patients.

Introduction

Chronic Exertional Compartment Syndrome (CECS) is a disabling condition that effects the lower leg, which was first described in 1945 [1]. CECS is characterized by lower leg pain after exertional activities, which is usually alleviated with rest [2]. If an individual continues exertional activity after the onset of pain, other symptoms may progress including increased intramuscular pressure, tightness, numbness, tingling, paresthesia, and muscular weakness [2]. While CECS is a relatively uncommon condition, researchers and healthcare providers believe it is likely under-reported [3]. A study of the US military population yielded an estimated average annual incidence of 0.49 per 1,000 person-years during the period of 2006 to 2011 [4]. Researchers consider this to be the best estimate of incidence for CECS in the absence of more accurate patient reported occurrence [5].

The majority of healthcare providers elect for conservative management of CECS initially [1]. Conservative treatment measures include oral nonsteroidal anti-inflammatory drugs, stretching, physical therapy, and activity modification [1]. However, it has been noted that activity modification may not be possible in populations such as competitive athletes and military service members [1]. Unfortunately, a systematic review of managing CECS patients revealed a 94% failure rate that resulted in patients opting for surgical intervention [6]. Since 1956, surgical fascial release has been the gold standard surgical intervention for CECS patients who have field non-operative treatment [7-9]. Despite being the gold standard, a

study of US military personnel who had undergone fascial release for CECS revealed a 45% recurrence rate, a 28% chance of being unable to return to full duty, a 6% chance of requiring revision surgery, and a 16% chance of complications [10]. The same study reported that 17% of fascial release patients ultimately required a medical discharge even after surgery [10].

Given the ineffectiveness of conservative measures as well as the high recurrence rate following surgery in physically active populations, it is imperative to develop additional management strategies for CECS. Previous case reports and preliminary studies have reported promising results for treating CECS with botulinum toxin-A injections [2,3,11-13]. Within the preliminary study of 25 anterior compartments and 17 lateral compartments, intramuscular pressure decreased by 63% ± 21% in the anterior compartment, and 68% ± 21% in the lateral compartment at follow up (range, 3-9 months) [11]. While these results have shown the potential for botulinum toxin-A to be a safe and effective alternative to surgical intervention, the researchers reporting their findings all stressed the need for more research [2,3,11-13]. Researchers have also stressed the need for providers to have a full understanding of the implications behind using botulinum toxin-A [2,3,11-13]. Therefore, the purpose of this review was to describe the currently available literature related to managing CECS patients with botulinum toxin-A injections.

Management of Chronic Exertional Compartment Syndrome with Botulinum Toxin-A

Presently, there are four commercially available preparations of botulinum toxin, each of which as its own potency and list of FDA approvals [14]. While traditionally used for aesthetic procedures such as treating wrinkles, a growing body of evidence suggests botulinum toxin may have a therapeutic role in treating musculoskeletal conditions [15]. In fact, the use of botulinum toxin has been described in treating neuropathic pain, popliteal artery entrapment, sternocleidomastoid fibrosis, and post-surgical abdominal wall musculature [16-19]. As with the previously mentioned studies on CECS patients, these authors also noted the need for further research on how to best utilize botulinum toxin for treatment musculoskeletal conditions.

Mechanism of action

Botulinum toxin-A is one of seven toxins produced by the bacterium *Clostridum botulinum* [15]. Although there are different preparations of botulinum toxin A, the mechanism of action is the same. When acting on motor neurons, botulinum toxin-A reduces muscle activity by binding to the motor endplate presynaptic receptors, thereby inhibiting the release of acetylcholine [20]. When acting on sensory neurons, botulinum toxin-A inhibits the release of pain modulating chemical mediators, including substance P, glutamate, capsaicin-induced duration of anesthesia, TRPV1 pathway, and calcitonin gene-related peptide at both the peripheral and central neuron level [20]. The muscle weakness and effects on voluntary muscle contraction following botulinum toxin-A treatment last approximately three months, and the autonomic pain modular effects are reported to last around six months [20]. While the effect of botulinum toxin-A on pain is fairly well understood, this does not account for any changes in compartmental pressure that have been observed when treating CECS patients.

Other hypotheses about the mechanism of action of botulinum toxin-A in CECS patients include the resulting muscle hypotonia following botulinum toxin-A injection [11,21,22]. This reduction in hypertrophy of the muscles within the affected lower leg compartment, would theoretically help reduce the symptoms of CECS [11]. Another plausible hypothesis is related to the muscle relaxation effects of botulinum toxin-A [11,23]. This reduction in muscle spasm would increase the length of time the muscle was relaxed, and subsequently improve blood flow to the muscles of the compartment [11]. Such an increase in blood flow would have potential modulary effects for any ischemic pain symptoms. It should be noted that all three of these theoretical modes of action may play a role in reducing the symptoms of CECS [11].

CECS recurrence rates following Botulinum Toxin-A treatment

To date, the majority of research on length of efficacy of treating CECS with botulinum toxin-A comes from case reports. These case reports show promising evidence for long-term impact on symptoms, with reports showing symptom alleviation for up to 36 months [2,12]. In spite of these findings, the authors of these case reports also noted that more extensive research needs to be conducted in order to produce a more definitive statement on the long-term efficacy of botulinum toxin-A for treating CECS.

One retrospective study that assessed the efficacy of botulinum toxin-A on CECS examined the cases of 16 patients (median age: 25.5) [24]. The study reported 68.75% efficacy, with seven patients experiencing complete relief of symptoms, and four patients experiencing partial relief of symptoms [24]. Patients with initial partial efficacy experienced a recurrence of pain at a median time of 2.25 months, while 57.1% of patients with complete relief of symptoms experienced recurrence of pain at a median time of 5 months [24]. Although there was a recurrence of symptoms in several patients, the authors did note that botulinum toxin showed at least moderate efficacy while patients suffered no major adverse effects [24].

Adverse effects

The most reported side effects from botulinum toxin-A injections appear to be injection site related [25]. These effects include soreness, edema, and ecchymosis [25]. Fortunately, true allergic reactions to botulinum toxin-A injections are a rare event [26,27]. There is some evidence to suggest that botulinum toxin-A injection increases the risk of granulomatous reactions at the injection site [28,29]. However, the authors noted that these infections may have been the result of a foreign body being introduced to the injection

site from a botulinum toxin-A diluent or lubricant material from the syringe [28,29].

Another extremely rare complication of botulinum toxin-A dosing is botulism. Botulism is characterized by systemic muscle weakness, fatigue, difficulty speaking, vomiting, abdominal swelling, and diarrhea, and can potentially be fatal [25]. Most authors agree that botulism toxicity generally results from the use of an unlicensed botulinum toxin product, or an overdose [25,30]. A systematic review of 63 cases of the systemic muscle weakness related to botulism found that, on average, the doses in affected patients were over three times the recommended dose for the preparation being used [31]. The same review suggested the most practical solution for reducing the risk of botulism is to use botulinum toxin-A preparations that are approved by the United States Food and Drug Administration (FDA) at recommended doses [31]. Regarding localized decreases in muscle strength, authors noted that these decreases did not result in functional impairment and patients were overall satisfied with the outcomes of their treatments [2,3,12]. A localized decrease in muscle strength in the lower leg compartments is clinically meaningful, as patients need to be counseled on the implications of potential changes to their strength, proprioception, and balance. However, these changes in muscle strength appear to be transient in nature [20].

Dosing

As previously mentioned, appropriate dosing in accordance with FDA recommendations is crucial for reducing the risk of adverse effects of botulinum toxin-A injection [31]. The protocol from the Uniformed Services University of the Health Sciences recommends delivering 25 units of onabotulinum toxin A into proximal and distal locations in each compartment for a total of 50 units per compartment [15]. The one exception within this protocol is for the superficial posterior compartment, for which 50 units is injected into the medial and lateral heads of the gastrocnemius and 50 units is injected into the soleus muscle [15]. The authors recommend that all injections be done under ultrasound guidance into the muscle belly [15]. Other protocols within case studies have used similar dosing schedules that have had similar results [2,12,13].

Summary

The purpose of this review was to describe the currently available literature related to the treatment of CECS with botulinum toxin-A.

While current studies do admit the need for further research to support the use of botulinum toxin-A for the treatment of CECS, the available literature does show promise [2,3,11,12]. Several case reports and a preliminary study have shown that botulinum toxin-A may be a safe and effective non-surgical alternative for the treatment of CECS [2,3,11,12]. Given that proper dosing and use of FDA-approved preparations significantly limits the risk of severe adverse outcomes, the use of botulinum toxin-A may be considered a relatively safe treatment option for CECS.

One of the most effective non-surgical interventions for CECS is relative rest or activity modification [1]. However, authors have noted that this is not a practical intervention for populations such as military service personnel and competitive athletes [1]. The surgical gold standard for treating CECS, fascial release, still has relatively high rates of decreased function and recurrence of symptoms. It is reasonable for clinicians to exhaust as many non-surgical interventions as possible [10]. Even with the potential for recurring symptoms after botulinum toxin-A injection, the relief of symptoms may allow an individual to achieve career or competitive goals prior to having to modify activity or elect for surgery. As with any medical procedure, informed patient consent is critical [32]. Patients should have a clear understanding of the benefits and risks of all management options for CECS. This allows patients to make the best possible decision according to their values.

In conclusion, the currently available evidence suggest that botulinum toxin-A injections may be a safe and effective non-operative treatment option for CECS. The risk of severe adverse effects is minimal when clinicians use appropriate dosing and FDA-approved preparations. Patient education, and communication before, during, and after treatment are critical for ensuring that patients' individual values have the best chance of being met by the chosen treatment option.

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