

Beyond the muscular effects – onabotulinumtoxinA injections for pain control in chronic knee osteoarthritis: a case report

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Abstract: We present a long-standing case of an 88-year-old woman with multiple comorbidities receiving intra-articular Botox[®] (onabotulinumtoxinA) injections for bilateral chronic knee osteoarthritis. She reported improved pain control and function supported by validated outcome measures.

Keywords: osteoarthritis, pain management, injection, Botox, knee

Introduction

Osteoarthritis (OA) is the most prevalent chronic articular disorder and a leading cause of chronic disability, affecting quality of life and functional status. It is characterized by progressive cartilage damage leading to changes in subchondral bone, osteophyte formation, muscle weakness and inflammation in synovial joints.^{1,2} With obesity and age being strong risk factors, the prevalence of knee OA has increased over the years.^{3,4} In 2011, it was recorded that about 13% of women and 10% of men aged 60 years or older have knee OA, and by the year 2020, it is estimated that 18.2% of the population (59.4 million Americans) will have some form of arthritis.^{3,4} Current options for care include analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs), weight loss, injection therapy, physical therapy and ultimately joint-replacement surgery.^{5,6} NSAIDs may be effective for pain control but are associated with gastric, cardiac and renal toxicities.^{5,6} Weight loss and physical therapy may not be sufficient alone for severe knee OA. Injection options including corticosteroids, viscosupplementation and platelet-rich plasma are limited by systemic side effects, cost and coverage. Joint-replacement surgery may be contraindicated or lose its efficacy over time with many patients seeing a return in pain. Therefore, safer less-invasive therapeutic options may be preferred.

Botulinum toxins (BoNTs) are well-studied neurotoxins produced by the Gram-negative anaerobic bacteria *Clostridium botulinum* and exists in seven different serotypes: A through G, with type A being the most potent.⁷⁻⁹ Each serotype is produced as a single polypeptide chain with a molecular mass of 150 kDa, consisting of a 50 kDa light chain and a 100 kDa heavy chain linked with a disulfide bond. BoNT interferes with neural transmission by blocking the release of acetylcholine (ACh), which is the principle neurotransmitter at the neuromuscular junction.⁷⁻⁹ Intramuscular administration leads to inhibition of the release of ACh causing temporary muscle paralysis.⁷⁻⁹ The 100 kDa heavy chain of the toxin attaches selectively and irreversibly to high-affinity

receptors in the presynaptic membrane of the nerve terminal, allowing the toxin complex to be taken up into the cell via endocytosis. Following this, the disulfide bond is cleaved, allowing the 50 kDa light chain to move to the presynaptic terminal. The light chain then cleaves off one of the soluble *N*-ethylmaleimide-sensitive fusion protein attachment receptor (SNARE) proteins, which are the proteins involved in vesicular trafficking and fusion with target membranes in a cell. BoNT-A and BoNT-E cleave synaptosomal-associated protein 25 kD (SNAP-25). BoNT-C cleaves both syntaxin and SNAP-25. BoNT-B, BoNT-D, BoNT-F and BoNT-G cleave vesicle-associated membrane protein (VAMP). This interferes with the exocytosis of cholinergic vesicles and leads to chemodenervation and reduced muscular contractions, thereby prolonging muscle weakness.⁷⁻⁹

Beyond muscular effects: antinociceptive effects

In addition to its muscle-paralyzing effects, there are potential antinociceptive effects of BoNT-A. These effects have been observed in the treatment of joint pain disorders and OA.⁹ Repeated injections of BoNT-A produced significant and durable reductions in joint pain severity in both animals and humans with no additional adverse systemic effects or loss of efficacy in function.¹⁰⁻¹⁴ Multiple potential antinociceptive mechanisms have been suggested on the basis of patient studies.¹⁰⁻¹⁴ It has been suggested that the analgesic effects may be multifactorial where BoNT-A may also suppress secretion of neurotransmitters. Experimentally, it has been revealed that BoNT-A suppresses other neurotransmitters such as norepinephrine while destroying SNARE complexes, which are normally required for vesicle fusion to release ACh.^{9,15-19} Therefore, it is proposed that BoNT-A serves as an anti-inflammatory and as an analgesic in addition to its suppressive properties of ACh by inhibiting secretion of other neurotransmitters and neuropeptides.^{9,15-19} Furthermore, it is observed that the analgesic effects of BoNT-A occur earlier and last longer, with greater magnitude than its effects of muscle paralysis.^{16,19} Studies have shown that BoNT-A reduces peripheral sensitization by inhibiting the release of neuronal signaling markers such as calcitonin gene-related peptide, glutamate and substance P, thus reducing *c-fos* gene expression.^{9,15-19} This is determined by Fos release by neuronal stimuli via expression of the *c-fos* gene. With BoNT-A inhibiting peripheral sensitization, it can also indirectly reduce central sensitization.^{9,15-19} This effect is applicable to patients with knee OA as repeated inflammation leads to excess stimulation of the central nervous system, ultimately

leading to more central sensitization.¹⁵ Based on these data, it is suggested that BoNT-A would be a viable therapeutic option for patients with knee OA to minimize pain and help maintain function.²

The specific aim of this case report was to document positive long-term analgesic benefits from repeated Botox[®] (onabotulinumtoxinA; OnaBTX-A) injections over 10 years on a patient with chronic knee OA.

Case study

An 88-year-old woman was first seen in 2006 with painful arthritic knees. Her past medical history included coronary artery disease, stroke with mild leg spasticity, Hashimoto's thyroiditis, Crohn's disease, diverticulosis, osteoporosis, macular degeneration and Bell's palsy. Her past surgical history included cholecystectomy and colostomy with reversal. At the time, the patient was taking mesalazine, venlafaxine, bisphosphonates, calcium lactate and vitamins B12 and D3. She was taking tramadol three times a day specifically for knee pain. She would take Tylenol #3 and Advil for breakthrough pain. On examination, stable vital signs were noted with a body mass index of 36. She ambulated slowly with a broad-based antalgic pattern using a single-tip cane. Standing X-rays and ultrasound studies of both knees (2007) revealed moderate degenerative changes in the medial compartment of the right knee and severe degenerative changes in the medial compartment of her left knee (Figure 1). They also showed a Baker's cyst in the right knee, which was also more painful. The risks and possible side effects of this novel treatment were thoroughly explained to the patient and her family. Having failed earlier corticosteroid injections and being unfit for surgery, she was agreeable and provided informed consent to receive OnaBTX-A injections for her OA knee pain and to have her case published. The signed consent for treatment and subsequent case publication are available in her chart. Full aseptic technique was used and incorporated buffered diluted lidocaine intradermal injection to make the procedure more comfortable. OnaBTX-A injections were started in the right knee with 50 units at a 2:1 dilution using a 22-gage 1.5-inch needle and ultrasound guidance (SonoSite MicroMaxx) with a medial subpatellar approach. Outcome measures recorded included numerical rating scale (NRS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores.

Results

After 2 months, she returned stating that the pain in her right knee was much improved. She also received the same



Figure 1 Technique used to inject OnaBTX-A into patient's knee using ultrasound.
Abbreviation: OnaBTX-A, onabotulinumtoxinA.

injection in her left knee and small doses ~10 units into her right tibialis posterior and medial gastrocnemius muscles for mild spasticity. The latter were stopped on subsequent visits as they were not found to be helpful. By March 10, 2009, the patient reported a 20%–30% improvement in her pain at each visit. She received on average 150 units of OnaBTX-A in each knee approximately every 3 months. NRS pain scores typically varied from a best of 3/10 (around a month post injection) to a worst of 9/10 (2 weeks prior to the next injection). With the pain relief, she lost 20 lbs by being more active and eating healthier. The patient experienced a plateau in pain relief by January 2011; the relief lasted for only 6 weeks. She started to use a wheeled walker. Her injection dose was also increased to 200 units in the left knee and 100 units in the right knee. She continued to receive such with OnaBTX-A regularly every 3 months. Results of each set of injections were also assessed using WOMAC (Table 1). In 2014, she was given a trial of intravenous (IV) lidocaine–ketamine infusion for neuropathic pain. She also continued to take Tylenol 3 and Aleve for breakthrough pain as needed and particularly when the OnaBTX-A treatments were wearing off. She also stopped injections for 6 months after suffering a myocardial infarction in May 2013. Her dosing was subsequently increased to 200 units in each knee by January 2011.

Table 1 WOMAC – LK3.1 comparison at two different visits.

	Pain (/20)	Stiffness (/8)	Difficulty performing daily activities (/68)
Section Visit 1			
Before OnaBTX-A injection	12	4	29 ^a
After injection	5	2	15 ^a
Section Visit 2			
Before OnaBTX-A injection	15	6	48 ^a
After injection	8	2	23 ^a

Notes: ^aTwo questions marked as non-applicable. Score out of 60.

Abbreviations: WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; OnaBTX-A, onabotulinumtoxinA.

Conclusion

To the best of our knowledge, the latest long-term retrospective study of OnaBTX-A for knee pain was for a period of 28 weeks in patients who have already had surgery.²⁰ Other studies looking at injections for OA without surgery followed patients from 12 to 17 weeks on average and saw effects lasting between 3 and 10 months. This case study is the first ever published study documenting long-standing pain relief and functional improvement with OnaBTX-A injections over a 10-year span (2007–2017). These treatments have improved this patient's quality of life by

helping her maintain independent activities of daily living. She was able to lose weight, stay active, avoid increases in oral pain medications and avoid knee surgery. To the best of our knowledge, this is the longest duration of a human patient receiving OnaBTX-A injections for chronic knee OA. This case report also noted that OnaBTX-A has a variable duration in pain relief of up to 3 months per injection and is safe and effective upon repeat injections. This suggests that in properly preselected individuals, OnaBTX-A is a viable option for therapeutic treatment of knee OA to decrease pain if other first- and second-line therapies have failed or are not options. In this patient's case, she was considered medically unstable to undergo surgical interventions. Randomized controlled trials (RCTs) have also been done on other OA joints.^{12,13,15} An RCT looked at the effect of BoN-BT on mice with induced knee OA, which demonstrated decreased pain behavior.¹⁴ Other case series have shown short-term analgesic effect of OnaBTX-A on patients with OA.^{8,11} Future research should include larger and longer term RCTs for chronic OA knee pain than the ones currently published. Further laboratory studies should also delineate the precise mechanisms beyond inflammation for knee OA. OnaBTX-A may be a safe and effective option for the patients living with chronic joint pain.

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Disclosure

The authors report no conflicts of interest in this work.

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