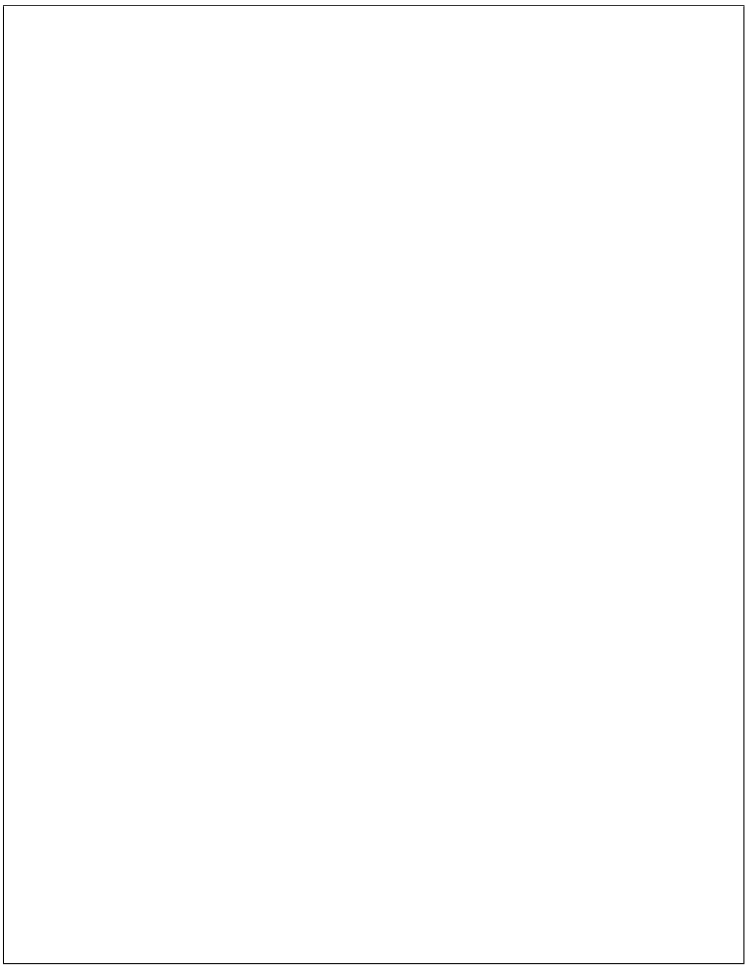

(This is a sample cover image for this issue. The actual cover is not yet available at this time.)

International Journal of Women's Dermatology 1 (2015) 167–169

Contents lists available at ScienceDirect

International Journal of Women's Dermatology

Botulinum toxin A injection for chronic anal fissures and anal sphincter spasm improves quality of life in recessive dystrophic epidermolysis bullosa

Cassandra Chaptini, MBBS [a,*], Genevieve Casey, MBBS [b], Adam G. Harris, MBChB [c,d], David Wattchow, FRACS [a], Lynne Gordon, FACD [a], Dedee F. Murrell, MA, BMBCh, FAAD, MD, FACD, FRCP [c,d]

[a] Flinders Medical Centre, Adelaide, Australia
[b] Women's and Children's Hospital, Adelaide, Australia
[c] Department of Dermatology, St. George Hospital, Sydney, Australia
[d] Faculty of Medicine, University of New South Wales, Sydney, Australia

ARTICLE INFO

Article history:
Received 2 July 2015
Received in revised form 12 August 2015
Accepted 12 August 2015

ABSTRACT

We report a 20-year-old female with generalized, severe, recessive dystrophic epidermolysis bullosa who developed secondary chronic anal fissures. This resulted in anal sphincter spasm and severe, disabling pain. She was treated with five botulinum toxin A injections into the internal anal sphincter over a period of 2 years and gained marked improvement in her symptoms. This case demonstrates the successful use of botulinum toxin A injections to relieve anal sphincter spasm and fissuring, with long-term improvement.

Introduction

Epidermolysis bullosa (EB) consists of a heterogeneous group of rare autosomal dominant or recessive disorders, characterized by epithelial fragility. Patients with recessive dystrophic epidermolysis bullosa (RDEB) often develop chronic constipation caused by painful defecation from blistering and tearing due to skin fragility, as well as by poor motility from opioid analgesia, which is frequently used in those with severe EB. As a result of straining, anal fissuring may further develop. Due to these painful fissures and ongoing constipation, chronic anal fissures and anal sphincter spasm may result. An anal fissure is a tear in the anoderm (squamous epithelium) distal to the dentate line. By definition, an acute anal fissure heals within 6 weeks with conservative local management, whereas a chronic anal fissure fails conservative management, requiring more aggressive measures.

This case demonstrates the successful use of botulinum toxin type A (BTX-A) to relieve anal sphincter spasms and improve chronic anal fissures from EB.

Case report

A 20-year-old female with generalized, severe RDEB gradually developed chronic anal fissures, resulting in severe anal sphincter spasms and severe, disabling pain. She also described chronic constipation and hemorrhoids. Her quality of life (QOL) was greatly diminished by this symptom (QOLEB pilot score of 42/75; Frew et al., 2009). She became profoundly depressed due to the pain and apparently insoluble problem.

She was born to nonconsanguineous parents and was diagnosed with RDEB as an infant. She had inherited two heterozygous deletion mutations in the COL7A1 gene, c[4918del] in exon 52 and [7634del] in exon 102, predicting two frameshift mutations, p. [Gly1640fs] and [Gly2545fs], leading to presumed downstream premature termination codons (Venugopal et al., 2013). This explained the lack of collagen VII expression in her skin on immunofluorescence mapping.

Blistering was extensive from early infancy, causing cutaneous scarring and mitten deformities of hands and feet. She developed known complications of EB, including squamous cell carcinoma, hepatic amyloidosis (Chaptini et al., 2015), premature and extensive dental caries, esophageal strictures, osteoporosis, hypogonadotrophic hypogonadism, and bilateral inferior exposure keratopathy. Previous procedures included surgeries to correct hand contractures, right lower-lid ectropion repair, and regular iron and blood transfusions for anemia. Medications included long-standing phenytoin 50 mg three times daily to aid wound healing, pantoprazole, cholecalciferol, estradiol/norethisterone, pregabalin, tramadol, oxycodone, and lactulose.

Physical examination revealed circumferential anal ulceration and an anal fissure at 6 o'clock. Internal hemorrhoids were present. Investigations revealed normochromic anemia (hemoglobin 85 g/L), hyponatremia (132 mmol/L), hypoalbuminemia (21 g/L), creatinine

* Corresponding author.
E-mail address: cassandra.chaptini@health.sa.gov.au (C. Chaptini).

http://dx.doi.org/10.1016/j.ijwd.2015.08.002

48 μmol/L, and liver function tests (LFTs) demonstrating a cholestatic picture. Anal manometry showed resting pressure 64 cmH_2O (range: 54-104), reduced squeeze pressure 147 cmH_2O (range: 179-317), and sphincter length 3.5 cm (range: 2.5-5).

Conservative measures for her anal fissures were trialed without success, including laxatives and a high-fiber diet. Glyceryl trinitrate 0.2% ointment and zinc barrier were also unsuccessful. When she was referred in November 2008 for participation in a cell therapy clinical trial in Sydney in 2009 (Venugopal et al., 2013), we were asked about how to manage the fissuring. After topical tacrolimus failed to relieve any inflammation, the suggestion was made to consider intramuscular BTX-A as a therapeutic intervention. Over a period of 2 years starting from age 19 years, she underwent five BTX-A injections into the internal anal sphincter (one injection approximately every 5 months), performed by a colorectal surgeon. In each case, a general anesthetic was used, and 50 units of BTX-A in 2.5 mL of normal saline were injected into the internal anal sphincter in all four quadrants. No complications or adverse effects were experienced. The patient experienced a 50% subjective improvement in her pain and spasms for at least 1 month after each injection, followed by residual improvement for many months. Four years after the cessation of injections, the patient's symptoms were still improved from baseline. She did not experience any fecal incontinence.

Discussion

Chronic anal fissures often complicate RDEB, as these patients develop constipation early on in life because of anal discomfort and medications. Once the tear in the anus mucosa occurs, it begins a cycle leading to repeated injury. The exposed internal sphincter muscle underneath the tear goes into spasm. As well as causing severe pain, the spasm pulls the edges of the fissure apart, impairing wound healing. The spasm also causes further tearing of the mucosa with each following bowel motion. In this case, BTX-A injections successfully relieved the anal sphincter spasm and pain secondary to recurrent anal fissures by interrupting the cycle of repeated injury.

Botulinum toxin, produced by *Clostridium botulinum,* blocks cholinergic nerve terminals and inhibits release of acetylcholine from nerve endings. It has been used to successfully treat certain spastic disorders of skeletal muscle, such as blepharospasm and torticollis, as well as wrinkles and spastic contractures in cerebral palsy.

Although there have been no documented cases of its use in EB for anal sphincter spasm or fissuring, it is commonly used to treat idiopathic anal sphincter spasm, typically given as injections around the anal canal (10 to 100 units total). It has also been reported to improve healing in patients with chronic anal fissures (Maria et al., 1998b). Despite variable doses and locations of the injection, four high-quality studies report its efficacy (Brisinda et al., 2004, 2007; Jost and Schrank, 1999; Maria et al., 1998a; Mínguez et al., 1999). The healing rate appears to be related to the dose and probably to the number of puncture sites (Maria et al., 1998a; Mínguez et al., 1999). In a randomized controlled trial, where 100 patients were treated with either BTX into the internal anal sphincter or 0.2% nitroglycerin ointment for 8 weeks, after 2 months the fissures were healed in 46 (92%) of 50 patients in the BTX group and in 35 (70%) of 50 in the nitroglycerin group ($p = 0.009$). Three patients in the BTX group reported adverse effects ($p < 0.001$) from mild incontinence to flatus that lasted 3 weeks after treatment but disappeared spontaneously (Brisinda et al., 2007). In another randomized controlled trial, 50 patients with chronic anal fissures received injections of 50 units of Botox formulation (group I), and 50 patients received injections of 150 units of Dysport toxin (group II; Brisinda et al., 2004). After 2 months, 46 patients in group I and 47 patients in group II had a healed scar. In group I patients, the mean resting anal pressure was 41.8% lower and the maximum voluntary squeeze pressure was 20.2% lower than the baseline value. In group II patients, the resting anal pressure and maximum voluntary squeeze pressure were 60.0 ± 12.0 mmHg and 71.0 ± 30.0 mmHg, respectively. There were no relapses in the 21 months of follow-up (Brisinda et al., 2004). Similarly, in a study where 30 patients with chronic anal fissures were randomized to intra-sphincteric BTX-A or saline injection, after 2 months significantly more patients who had received BTX-A had healed (73% versus 13%; Maria et al., 1998a). This was supported by another study where repeated BTX-A therapy was used in 50 patients who failed initial (insufficient) BTX-A treatment. Nineteen of 20 patients (95%) treated with five units of BTX-A were pain-free within 1 week, and healing was observed in 70% by 3 months. Twenty-two of 30 patients (73%) treated with 10 units of BTX-A were pain-free within 1 week, and 19 (63%) demonstrated healing after 3 months (Jost and Schrank, 1999).

Botulinum toxin injections have been used twice before in patients with EB in the literature for reasons other than anal sphincter spasm. BTX-A has been used to treat palmar and plantar hyperhidrosis, which was found to be effective and safe (Schnider et al., 1997; Vadoud-Seyedi, 2004). As hyperhidrosis contributes to frictional trauma and the development of blisters in EB simplex (EBS), it was thought that BTX-A may have a therapeutic role in this condition. Hence, BTX-A was used in a double-blinded-study of a 43-year-old woman with EBS, localized type, to treat blisters and erosions on the plantar aspect of her feet (Abitbol and Zhou, 2009). The foot treated with BTX-A had decreased pain and perspiration and a 64% decrease in blister formation after 3 months compared to the control foot, which received normal saline injections (Abitbol and Zhou, 2009). Furthermore, a retrospective study of 14 patients (6 with EBS) with foot blisters who had received botulinum toxin therapy showed that 13 (93%) patients reported reduced blistering and pain, with a mean effect of 3 months (Swartling et al., 2010). The mechanism of action of BTX-A in the above cases is via blocking the autonomic cholinergic junctions of the post-ganglionic sympathetic fibers to the sweat glands, thus preventing hyperhidrosis.

The mechanism of action in improving chronic anal fissures and spasm, as depicted in this case, is likely mainly due to cholinergic nerve terminal blockade, preventing spasm, as well as blockade of the post-ganglionic sympathetic fibers, preventing sweating, and subsequent fissuring.

The main adverse effects after local injection of BTX-A are weakness in the muscles adjacent to the treatment sites and, in the perianal area, fecal incontinence. Beneficial effects have been shown to last from 4 months to 1 year (Swartling et al., 2010). The long-term outcome of BTX-A treatment has not been well described in the literature; recurrence may be common. The report with the longest follow-up (42 months) showed that in 57 patients who had healed anal fissures from BTX 6 months after injection, a recurrent fissure was observed in 22 patients (42%; Minguez et al., 2002). However, in the case described, long-term benefits remained after 4 years, indicating that this is a useful adjunctive treatment for rare patients with these disabling symptoms.

Conclusion

This case demonstrates the successful treatment of chronic anal fissures and anal sphincter spasm with botulinum toxin A injections, with nil adverse effects. Botulinum toxin A injections should be considered as a treatment for anal sphincter spasm secondary to recurrent anal fissures in EB when conservative measures fail.

Acknowledgments

The open access publication charges for this article were supported by the Caroline Quinn Trust Fund and the Australasian Blistering Diseases Foundation.

References

Abitbol RJ, Zhou LH. Treatment of epidermolysis bullosa simplex, Weber-Cockayne type, with botulinum toxin type A. Arch Dermatol 2009;145(1):13–5. http://dx.doi.org/10.1001/archdermatol.2008.546.

Brisinda G, Albanese A, Cadeddu F, Bentivoglio AR, Mabisombi A, Marniga G, et al. Botulinum neurotoxin to treat chronic anal fissure: results of a randomized "Botox vs. Dysport" controlled trial. Aliment Pharmacol Ther 2004;19(6):695–701.

Brisinda G, Cadeddu F, Brandara F, Marniga G, Maria G. Randomized clinical trial comparing botulinum toxin injections with 0.2 per cent nitroglycerin ointment for chronic anal fissure. Br J Surg 2007;94(2):162–7.

Chaptini C, Casey G, Harris AG, Murrell DF, Gordon L. Recessive dystrophic epidermolysis bullosa complicated by secondary hepatic amyloidosis. JAAD Case Rep 2015;1(6):337–9.

Frew JW, Martin LK, Nijsten T, Murrell DF. Quality of life evaluation in epidermolysis bullosa (EB) through the development of the QOLEB questionnaire: an EB-specific quality of life instrument. Br J Dermatol 2009;61(6):1323–30. http://dx.doi.org/10.1111/j.1365-2133.2009.09347.x.

Jost WH, Schrank B. Repeat botulin toxin injections in anal fissure: in patients with relapse and after insufficient effect of first treatment. Dig Dis Sci 1999;44(8):1588.

Maria G, Brisinda G, Bentivoglio AR, Cassetta E, Gui D, Albanese A. Botulinum toxin injections in the internal anal sphincter for the treatment of chronic anal fissure: long-term results after two different dosage regimens. Ann Surg 1998;228(5):664–9.

Maria G, Cassetta E, Gui D, Brisinda G, Bentivoglio AR, Albanese A. A comparison of botulinum toxin and saline for the treatment of chronic anal fissure. N Engl J Med 1998;338(4):217–20.

Mínguez M, Melo F, Espí A, Garcia-Granero E, Mora F, Lledo S, et al. Therapeutic effects of different doses of botulinum toxin in chronic anal fissure. Dis Colon Rectum 1999;42(8):1016–21.

Minguez M, Herreros B, Espi A, Garcia-Granero E, Sanchiz V, Mora F, et al. Long-term follow-up (42 months) of chronic anal fissure after healing with botulinum toxin. Gastroenterology 2002;123(1):112.

Schnider P, Binder M, Auff E. Double-blind trial of botulinum A toxin for the treatment of focal hyperhidrosis of the palms. Br J Dermatol 1997;136(4):548–52.

Swartling C, Karlqvist M, Hymnelius K, Weis J, Vahlquist A. Botulinum toxin in the treatment of sweat-worsened foot problems in patients with epidermolysis bullosa simplex and pachyonychia congenita. Br J Dermatol 2010;163(5):1072–6. http://dx.doi.org/10.1111/j.1365-2133.2010.09927.x.

Vadoud-Seyedi J. Treatment of plantar hyperhidrosis with botulinum toxin type A. Int J Dermatol 2004;43(12):969–71.

Venugopal SS, Yan W, Frew JW, Cohn HI, Rhodes LM, Tran K, et al. A phase II randomized vehicle-controlled trial of intradermal allogeneic fibroblasts for recessive dystrophic epidermolysis bullosa. J Am Acad Dermatol 2013;69(6):898–908. http://dx.doi.org/10.1016/j.jaad.2013.08.014.