A Case Report of Cryoneurolysis With Factor VIII Administration for Cerebral Palsy-related Spasticity in a Patient With Hemophilia A

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ABSTRACT: Spasticity affects up to 80% of individuals with cerebral palsy and can lead to pain and difficulties with performing activities of daily living. If left untreated, spasticity can progress to contracture and neuro-orthopedic deformities. Cryoneurolysis is an emerging and mini-invasive ultrasound-guided technique that causes secondary axonotmesis of peripheral nerves through the formation of an ice ball and may result in months to years of improved range of motion and reduced pain in patients with spasticity. However, the safety of cryoneurolysis has not yet been established in patients with an increased bleeding risk secondary to Hemophilia A. We present a case of cryoneurolysis for cerebral palsy-related spasticity in a 14-year-old male with hemophilia A who previously had minimal benefit from botulinum toxin for increased elbow and wrist flexor tone with contracture. Fifteen minutes prior to cryoneurolysis, an IV infusion of 2000 IU of recombinant antihemophilic factor (FVIII) was administered for bleeding prophylaxis. Targets were identified with ultrasound guidance and nerve stimulation and cryoneurolysis was performed without bleeding complications or adverse events. There was an immediate improvement in tone and range of motion that was maintained at 3- and 8-month follow-ups with reported increased left arm function. This case suggests that cryoneurolysis is an effective mini-invasive procedure for spasticity that improves tone and range of motion and is safe for use in patients with Hemophilia A who receive adequate Factor VIII prophylaxis.

KEYWORDS: Case report, cryoneurolysis, Factor VIII, hemophilia A, spasticity

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Spasticity affects up to 80% of people with cerebral palsy and can lead to pain, difficulties performing activities of daily living (ADLs), and decreased quality of life.[1] If left untreated, spasticity can progress to shortening and contracture of muscle resulting in neuro-orthopedic deformities. A mainstay of spasticity treatment is oral baclofen, but due to poor blood-brain barrier permeability high doses are often required, leading to decreased tolerability due to its side effects of somnolence, asthenia, and headache.[2]

Focal spasticity is commonly treated with botulinum toxin (BoNT), which acts by blocking presynaptic acetylcholine release to help reduce tone.[3] The effects of BoNT peak at 3 to 4 weeks and patients often require repeat treatment every 3 to 4 months.[2] In people with hemophilia (PwH), an X-linked recessive condition causing deficiency in coagulation factors,[4] spasticity management interventions such as repeat BoNT injections pose an increased risk of bleeding and hematoma. However, a 2018 case report showed that BoNT was safe and effective for post-stroke spasticity in a patient with hemophilia A who received prophylactic intravenous recombinant human coagulation Factor VIII (FVIII) infusion and successfully underwent 3 injection cycles over 9 months without any adverse bleeding complications.[5] Still, repeat BoNT treatment can present a financial burden to patients and the healthcare system. Additionally, procedural sedation may be required in pediatric cases, thus increasing children's time away from school and parents' time away from work. As such, we sought to assess if cryoneurolysis is a safe and effective alternative for a pediatric male patient with hemiplegia and hemophilia A.

Cryoneurolysis is a novel minimally invasive procedure that has been well-established for reducing pain[6] and recently has demonstrated effectiveness in reducing spasticity.[7] Under ultrasound guidance, a peripheral nerve is targeted with a specialized probe and using interstitial fluid and the Joule-Thomson effect of gas expansion, an iceball between −66°C and −88°C is created.[8] Formation of this iceball causes axonotmesis while preserving the epineurium and perineurium to provide a pathway for axonal regeneration. Recent case studies have shown that cryoneurolysis improves muscle range of motion for 6 to 9 months.[9,10] However, the safety of cryoneurolysis has not yet been investigated in PwH.

Case Report

A 14-year-old male presented with a history of hemophilia A (FVIII <0.5%), left hemiplegia secondary to neonatal intracranial hemorrhage, and a seizure disorder well controlled on

levetiracetam. Hematology had followed the patient since 2014. Bleeding had been well-controlled on emicizumab, a FVIII mimetic. At the age of 10 years, the patient underwent a right tibial epiphysiodesis with a hinge plate procedure for leg length discrepancy and dynamic inversion deformity. This was followed by a left-sided split tibialis anterior tendon transfer to lateral cuneiform, Jones transfer of extensor hallucis longus to the first metatarsal neck, interphalangeal joint fusion of the first toe, Vulpius Achilles tendon lengthening, and plantar fascial release at the age of 12 years. Preoperative FVIII infusions were administered prior to each surgery and the patient did not have any adverse bleeding events or complications.

The patient was referred to an outpatient rehabilitation clinic for decreasing left arm function due to increased tone at the elbow and wrist. The patient was independent with ADLs, ambulating with a cane due to visual impairment, and excelling in school. However, the patient had increased difficulties with hand opening and wrist extension due to a worsening wrist flexion contracture. There was also limited elbow extension from increased elbow flexor tone. Stretching and physiotherapy had become increasingly difficult and painful, and the patient was no longer tolerating bracing. The patient was previously treated with BoNT with only a short duration of mild benefit (Table 1).

On physical examination, the patient had 120° of active and passive elbow flexion but lacked 60° of active elbow extension and 35° of passive elbow extension due to elbow flexor tightness (Modified Ashworth Scale [MAS] 3; Table 2). There was a wrist flexion contracture, with limited passive extension to 10° above neutral (MAS 3), and minimal active and passive finger extension (Table 2).

Table 1. Previous botulinum toxin targets and dosage.

DATE	ONABOTULINUM TOXIN A TARGETS AND DOSAGE
22-July-2015	• Biceps: 40 U • Flexor digitorum superficialis: 20 U • Flexor carpi radialis: 20 U • Pronator teres: 20 U
20-January-2016	• Biceps: 40 U • Flexor pronator mass[a]: 60 U
23-November-2016	• Biceps: 50 U • Flexor pronator mass[a]: 50 U • Tibialis posterior: 50 U • Gastrocsoleus complex: 50 U
19-April-2017	• Biceps: 30 U • Flexor pronator mass (distributed between finger flexors, common wrist flexors, and PT)[a]: 70 U • Gastrocnemius: 100 U
06-December-2017	• Biceps: 50 U
09-May-2018	• Biceps: 50 U • Flexor pronator mass[a]: 50 U

[a]Wording used by the surgeon.

Methods

This study follows the Case Reports (CARE) guidelines and reports the required information accordingly. Institutional research ethics board approval was not required. Informed consent was obtained for the procedures, images, videos, and preparation of this manuscript.

Based on the clinical assessment, the left *biceps brachii*, *brachialis*, *flexor carpi radialis (FCR)*, and *flexor carpi ulnaris (FCU)* were identified as potential targets for treatment.

Clinical evaluation and diagnostic nerve block

Diagnostic nerve blocks (DNB) were performed under ultrasound (US) and nerve stimulation guidance using a 25-G stimulating needle. One cc of 2% lidocaine was administered to the musculocutaneous motor nerve branches to the biceps brachii and brachialis, median nerve branches to the FCR, and ulnar nerve branches to the FCU. There was no undesirable loss of sensation or function after the DNB. No adverse events were reported during or immediately after the procedure. Repeat examination showed improved speed of elbow movements, decreased spasticity at the wrist flexors, and an elongated resting arm position. The family identified a skin rash on the arm following the procedure and were uncertain if it was from bandage and electrode adhesives or lidocaine, as the patient has allergies to many irritants. Education on cryoneurolysis was provided and informed consent was obtained after discussing the risk of pain, bleeding, and infection.

Assessment of spasticity and range of motion

Baseline and post-procedure spasticity was measured and reported using the MAS and the Modified Tardieu Scale, both of which are validated clinical assessment tools for spasticity.[11-13] These include the angles (X) of maximum passive ROM $X(_{V1})$ about the joint and the angle of catch with quick movement $X(_{V3})$. Range of motion assessments were completed by the same assessors and measured using a goniometer at each follow-up visit to improve consistency in readings.

Cryoneurolysis

Prior to the procedure, the patient was seen by hematology for bleeding prophylaxis recommendations. No modifications to his emicizumab regime were made. IV access was obtained under US guidance and the patient underwent an IV infusion of 2000 IU of recombinant antihemophilic FVIII (Eloctate). Adequate sedation and analgesia were obtained using nitrous oxide gas (Pronox) and fentanyl. Due to a chlorhexidine allergy, the skin was cleaned with 70% isopropyl alcohol swabs and was briefly covered with ice rather than injecting lidocaine subcutaneously.

Table 2. Elbow and wrist joint range of motion measurements for baseline and post-procedure follow-ups.

MOVEMENT AT JOINT		BASELINE	3-WEEK FOLLOW-UP	3-MONTH FOLLOW-UP	8-MONTH FOLLOW-UP
Left elbow extension	X(V1)	−35°	−35°	−30°	−30°
	X(V3)	−60°	No	−70°	−100°
	AROM	−140° to −60°	−140° to −40°	−140° to −40°	−140° to −50°
	MAS	3	2	2	2
Left wrist extension	X(V1)	+10°	+40°	+40°	+30°
	X(V3)	−45°	−15°	−10°	−15°
	AROM	No active movement	No active movement	No active movement	No active movement
	MAS	3	2	2	2

Abbreviations: AROM, active range of motion; MAS, Modified Ashworth Scale.
Measured within the patient's available ROM. X denotes the angle. $X_{(V1)}$ denotes the maximal range of passive range of motion. $X_{(V3)}$ denotes the angle of catch or clonus.

A 16-G Angiocath was inserted into the skin under US guidance to guide the cryoprobe, protect the skin from potential cold-related adverse events, and increase ultrasound echogenicity. The cryoneurolysis probe was inserted using the handheld Iovera System (Iovera System 190 Smart Tip; Iovera, Pacira, USA).

Three insertion points were made at the:

1. Proximal medial upper arm to target biceps brachii
2. Distal medial upper arm to target brachialis
3. Anterolateral forearm several centimeters distal to the elbow to target FCR and palmaris longus. The probe was then advanced medially into the FCU muscle belly.

Individual nerve targets were identified with ultrasound and known anatomy, with confirmation using electrical stimulation of less than 1 mA at 1 Hz. The left intramuscular musculocutaneous nerve branches of the biceps brachii and brachialis, median nerve intermuscular branches of the palmaris longus and FCR, and ulnar nerve branch to the left FCU were each targeted with a single 106-second cycle (Figure 1; Supplemental Video 1).

Results

The patient reported cramping and burning pain during the procedure, which was managed with further fentanyl administration. After cryoneurolysis, ice and compression were applied to the puncture sites. There was no evidence of acute bleeding. The patient developed his customary rash associated with procedures on his left arm and was obtunded and agitated following procedural sedation, both of which were resolved within 30 minutes. The procedure was otherwise well tolerated, and no adverse effects were reported. There was no bleeding or bruising reported the following day with a photograph sent by the family. The patient was encouraged to continue with his regular physiotherapy and music therapy routine, with more focus on stretching and exercise based on the available guidelines.

At his 3-week follow-up visit, the patient reported increased left arm use for functional tasks including dressing and holding objects. Both the patient and examining physician noted the left arm hanging lower at rest and during walking. On examination, there was reduced flexor tone at the elbow (MAS 2) and wrist (MAS 2). Active left elbow extension range of motion improved by 20° and passive wrist extension improved by 30° (Table 2; Supplemental Video 2). A wrist hand orthosis and an elbow extension orthosis were prescribed.

At 3 months, results were sustained for both the elbow and wrist tone, as well as range of motion, with an additional 5° improvement in passive elbow extension (Table 2). The patient's family reported greater ease of fingernail trimming and that the patient had improved ability to lift and carry items. They had not obtained the elbow brace, and compliance for the wrist hand orthosis was not desired by the patient.

At 8 month, active elbow extension remained improved, and passive wrist extension was 10° greater than baseline (Table 2). The patient continued to report reduced left elbow stiffness and sustained functional improvements. However, they were not using a wrist brace and the patient noted stiffness returning to the wrist. The examining physician noted that a repeat procedure was not needed at the time.

Discussion

In this case study, we demonstrated the safety of cryoneurolysis in a patient with hemophilia A. Cryoneurolysis is a drug-free intervention that can selectively target and reversibly disrupt nerve conduction, thus causing minimal damage to surrounding

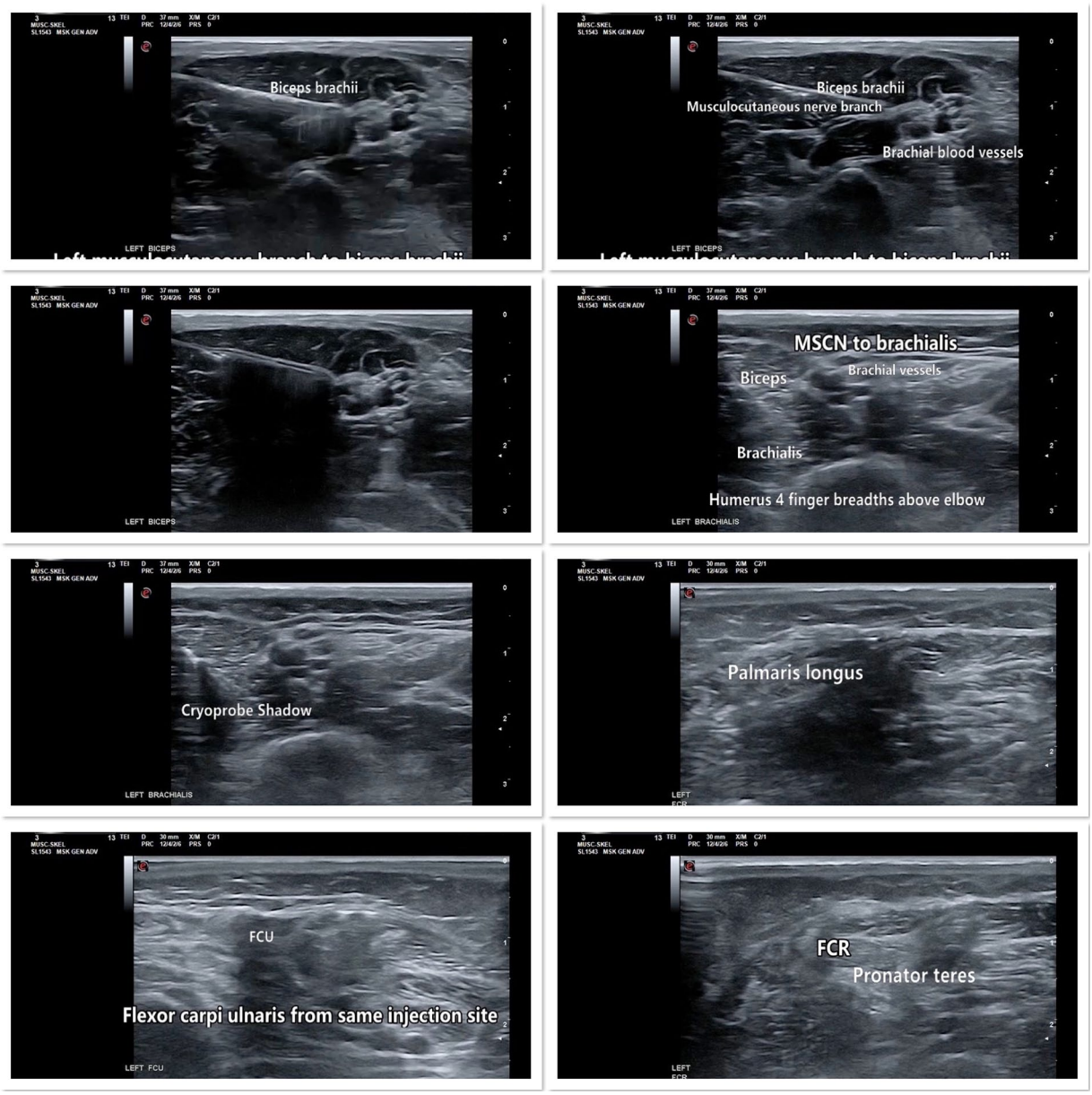

Figure 1. Ultrasound images of the upper limb during cryoneurolysis.

tissue and vasculature in animal studies.[14] Recently, Winston and colleagues have published numerous case reports that demonstrated the effectiveness of cryoneurolysis for spasticity[7,9,15-20] following the initial use of the technique in 1998 for adductor spasticity and obturator neuralgia.[21] Multiple reports have demonstrated that cryoneurolysis has prolonged effects on spasticity[7,15,17] and benefits from a low risk profile with adverse events of local skin infection, bruising, swelling, nerve pain, or dysesthesia affecting approximately 3% to 4% of patients.[6,22] In this case, the patient developed pain during the procedure, but no other adverse events were reported. This mini-invasive procedure helps reduce complication risk and has a minimal recovery period, enabling patients to quickly return to daily functioning and limit time away from school and work.[6,22]

Following cryoneurolysis the patient experienced an objective improvement in elbow and wrist extension and sustained functional improvements at multiple follow-up appointments. These functional gains translated into improved independence in ADLs and enhanced quality of life for the patient and their family. At 8-month follow-up, benefits were largely maintained, compared to the typical 3- to 4-month interval with BoNT.[5,23] In addition, costs associated with the cryoneurolysis probe and nitrous oxide gas are less than the cost of injecting 100 U of onabotulinum toxin A, previously given in just 1 treatment cycle for the patient's spasticity. As such, cryoneurolysis may be beneficial from both a time and financial standpoint with reduced treatment frequency and equipment costs.

Currently, there is limited literature regarding the safety of BoNT in PwH. The World Federation of Hemophilia (WFH) has not published specific guidelines for BoNT use in PwH. However, Shin et al. referenced the WFH guidelines for "minor surgery" to inform their FVIII infusion protocol. After

administering a pre-procedure bolus and smaller post-procedure infusions 1 and 2 days later no bleeding complications arose.[5,24] Conversely, a 2015 case report described a patient with hemophilia who developed 5 days of hematuria after BoNT treatment for BoNT for upper limb spasticity without prophylactic factor replacement. Although, after FVIII infusion the patient's hematuria resolved.[25] Still, due to an increased risk of hematoma and pseudotumors and a lack of well-designed BoNT safety studies, a 2017 hematology report recommended avoiding BoNT in PwH altogether.[26]

Compared to BoNT, cryoneurolysis requires fewer percutaneous needle insertions and therefore may result in an overall decreased bleeding risk. However, cryoneurolysis needs to be approached cautiously in patients with bleeding disorders.[27] Given the patient's bleeding risk, use of a 16-G catheter, and 106-second ablation cycle, the procedure's safety was a significant consideration. Here, our patient was successfully treated with a single pre-procedural FVIII infusion after consultation with their hematologist. With prophylactic FVIII and careful target localization with the use of US guidance and nerve stimulation, no bleeding complications arose from the procedure.

When used early and in conjunction with conservative measures such as stretching, physical therapy, bracing, and spasticity-reducing medications, BoNT is intended to help prolong the need for spasticity-related surgery.[28-33] Although recent studies show that surgery can be safely performed in most PwH on emicizumab,[34] advanced preoperative planning is required.[35] Moreover, surgery should ideally be performed at a center with access to hematology and other necessary resources.[35] These measures limit access to patients in remote settings and increase healthcare spending. Beyond this, surgery can require extensive tissue manipulation resulting in days to weeks of postoperative pain, as well as longer recovery periods to allow for tissue healing. Future research may wish to evaluate the potential for cryoneurolysis to prolong the need for spasticity-related surgery, which may help manage PwH increased bleed risk, reduce access barriers, and alleviate healthcare system costs.

A final consideration is why cryoneurolysis was chosen as the neurolytic agent. When injected, phenol induces chemical destruction of nerve tissue. However, it is not selective and can cause myonecrosis and nonselective nerve damage in the vicinity. Phenol can occlude microcirculation near the nerve, leading to thrombosis, vascular fibrosis, and localized tissue damage. This may contribute to the release of neurotrophins, substances involved in nerve regrowth and associated with painful neuromas and neuralgia.[36] Unlike phenol, cryoneurolysis spares surrounding structures, including blood vessels, which are a protective heat sink.[37] Furthermore, they are not thrombosed, as is described with phenol.[36,37] As the epineurium and perineurium are preserved, no noxious substances are released.[14]

While more research is required, cryoneurolysis may offer a safe and cost-effective alternative to BoNT in spasticity management for PwH. Additionally, further investigation will be required to better understand the bleeding risk associated with cryoneurolysis in PwH.

Limitations

This case report outlines the experience of a single patient with hemophilia A, thus restricting the generalizability of these findings. The outcomes observed in this report may not reflect the experiences of all PwH or related conditions and individual patient responses to cryoneurolysis can vary widely. Furthermore, use of MAS scores is a limited clinical measure given its subjective nature. Additional research is needed to determine how different patient factors such as age, severity of spasticity, and overall health, influence treatment outcomes. To validate these findings and confirm their relevance to a broader population, future studies with larger and more varied cohorts are essential.

Conclusion and Clinical Relevance

The minimization of bleeding risk is a primary concern with PwH especially in regard to invasive medical interventions. This is the first case report showing that cryoneurolysis is a safe and effective treatment for spasticity in PwH, demonstrating the potential for long-term functional improvements and improved quality of life in this population.

Author Note

This has been presented as a case report at the 2024 World Congress of Neurorehabilitation, and the 2024 Canadian Association of Physical Medicine & Rehabilitation conference.

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None required.

Data Availability

Data access is available upon request.

Consent for Publication and Ethical Approval

This is a case report. It received institutional Ethics approval number H23-00533. A retrospective analysis of patients undergoing cryoneurolysis; Patient's characteristic, targeted nerves, and cost analysis. The family gave additional consent for publication. All authors give consent to publish.

Consent to Participate

Written and verbal informed consent was obtained from the participant.

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Supplemental Material

Supplemental material for this article is available online.

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