PROTOCOL TITLE	Effect of the cryoneurolysis on pain and positioning in patients with wrist and hand contracture.
PROTOCOL NUMBER	H22-03181
VERSION 1.0	Jan 9,2023
Principal Investigator	Paul Winston MD, FRCPC Department of Medicine Victoria General Hospital-1 Hospital Way Victoria, BC V8Z 6R5 Email: paul.winston@viha.ca Phone: 250-884-8872 FAX: 250-727-4221
Co-investigators	Mahdis Hashemi MD, Research Coordinator Victoria General Hospital-1 Hospital Way Victoria, BC V8Z 6R5

Background and Justification:

Contracture is defined as a limitation of the maximum passive range of motion (ROM) of a joint due to shortening and changes of periarticular soft tissue structures; including tendons, muscles and ligaments.[1] Once a contracture is present, management options are limited and mainly includes surgery. Contracture contributes to the increased disability, decreased functional ROM, decreased functional activities of daily living and increased pain.[2] The incidence of contracture one year after spinal cord injury has been reported to be as high as 66%, including 33% in elbow and forearm and 41% in wrist and hand.[3] It may be present in up to 28% of patients within 3 months after stroke with wrist as the most affected joint.[4] At 6 months, the incidence increases to 50%.[5]

Contracture is not just limited to spasticity. It is seen in many neurogenerative and musculoskeletal conditions and is most commonly found in the nursing home population, with a prevalence of 61.2% in older adults in nursing homes in the United States.[6] In Germany, contractures were also seen in 55% of nursing home residents with significant medical and functional consequences.[7] In France, 8.8% of older adults in nursing homes had a claw hand from contracture of wrist or finger flexors (claw hand).[8]

While contracture can be the primary cause of severe pain, the presence of pain and loss of dexterity significantly contribute to the development of the contracture. [4]Thus, pain management is a crucial part of contracture treatment. There are many guidelines for pharmacological and non-pharmacological treatment of contracture and associated pain such as botulinum toxin injection, physiotherapy, stretching, positioning and surgery. While surgery has been recommended as the most effective treatment, it requires to be done under general anesthesia and in an in-patient setting, which impose many risks to patients especially in frail older population most likely to require contracture management. [9]

Our group have been global pioneers in the use of cryoneurolysis to manage spasticity and pain due to severe spasticity and contracture. (clinicaltrials.gov NCT04670783, NCT05147441, NCT04907201) [10,11,12,13,] The process first involves isolating the targeted nerves that innervate the targeted muscles with ultrasound guidance (US) and e-stimulation (e-stim) for motor nerves and mixed motor sensory nerves for pain. We are completing enrollment on four studies with over 100 patients enrolled, in both the outpatient and in-patient settings. Our published protocol shows a unique goal for cryoneurolysis, to both decrease the tone and pain. The 2019, French Clinical guideline for peripheral motor nerve blocks in a PRM setting,[14] established the first expert opinion paper for utilizing the DNB in spasticity and pain management. Through temporary paralysis of a muscle by blocking the motor branches of the nerve and blocking the sensory fibers by targeting the sensory fibers of related nerve, the DNB can result in reduction of pain and muscle tone even in what may have been thought to be a fixed contracture. The French guidelines claim the DNB forms the basis of optimal muscle selection and whether to proceed to BoNT, neurectomy, or for a more refractory muscle for surgical muscle lengthening.

In our protocols, after a successful DNB to reduce pain and the muscle tone, a patient is offered cryoneurolysis. This mini-invasive percutaneous procedure is performed using a small 20-gauge cryoprobe. Cryoneurolysis has been used for over fifty years for pain relief from months to years when used for sensory nerves. [15,16] Cryoneurolysis occurs due to the process of throttling a gas through an orifice from high to low pressure resulting in a rapid expansion of the gas and a drop in temperature, known as the Joule-Thomson effect. The rapid cooling generates an ice ball or oval between 3.5 and 18 mm that is formed at the tip of the with compressed N2O at temperatures typically at -88° C. The ice causes a targeted zone of axon and myelin disruption, resulting in loss of axon continuity due to Wallerian degeneration of the targeted nerve extending outward from the lesion. However, the basal lamina, epineurium and perineurium of the targeted nerve remain intact and serve as a tube for neural regeneration.[17,18] For over four years we have been tracking outcomes of cryoneurolysis. Our initial results are published as cases but are also in pre-publication prospective studies revealing significant pain reduction. We have published several manuscripts on cryoneurolysis.[10,11,12] Several book chapters and a textbook are in in publication or published.[9] Cryoneurolysis is cheaper, faster, and less invasive than surgical intervention for the treatment of severe spasticity and contracture associated pain.

In Canada, one vial of BoNT costs approximately $400. The typical patient can be injected with 400 units up to four times a year, thus $6400 a year, indefinitely. Patients are often treated outside the product monograph, off label, with 600 units, and for over ten years, thus treatments may cost many tens of thousands of dollars. A one-time treatment with cryoneurolysis would cost approximately $725 and could potentially last for years, more in line with surgical neurectomy or tendon lengthening, yet with no recovery time surgery.

After witnessing the reduction in pain from contracture with cryoneurolysis in our experience, we propose to measure its effect prospectively and systematically on pain reduction in patients with wrist and hand severe spasticity or contracture due to any underlying disease. These patients are already undergoing cryoneurolysis in our clinic, with our island health allotment of cryoneurolysis equipment as well as those that were enrolled in our now completed upper extremity study. All patients are deemed candidate for cryoneurolysis based on their positive responses to DNB.

Purpose:

The purpose of this pilot study is to evaluate if cryoneurolysis will be effective to control pain in patient with wrist and hand contracture. Also, to evaluate if there is any correlation between pain reduction with improvement in ROM and spasticity reduction in participants who are already candidate for DNB and cryoneurolysis. The results will increase our knowledge about cryoneurolysis and if it can be used just for pain control and in patients with fixed contracture.

Objectives:

1. To evaluate the effect of cryoneurolysis on pain in patients with hand and wrist contracture.
2. To assess any changes in wrist and fingers ROM and spasticity in patients with hand and wrist contracture.
3. To evaluate if there is any correlation between changes in ROM and spasticity with pain
4. To record any changes in pain medication that they receive for pain management.

Hypotheses:

1. Cryoneurolysis can be used as a pain control tool in patients with wrist and hand contracture.
2. Cryoneurolysis can improve wrist and finger ROM and spasticity in patients with hand and wrist contracture.
3. Pain reduction after cryoneurolysis is independent from the increase in ROM and spasticity reduction.
4. The needs for pain medication will decrease after the procedure.

Research Design:

This project constitutes a single-centre, prospective cohort study. Data collection will occur at the Victoria General Hospital (VGH) spasticity clinic. Patients with severe spasticity and contracture are referred to this clinic for different procedures including cryoneurolysis. This study will not interfere or change the patients' medical care. We will do the assessments for the patients who are already candidates for this procedure as a

part of their treatment, besides other provided medical cares and have been accepted to receive it.

All measurements are a part of routine assessment for patients with severe spasticity and contracture.

The evaluation will be done for them after receiving oral and written consent.

Methods:

The assessment will be done at baseline, 2 weeks, 1 month and 3 months after being enrolled in the study in the same day of their appointments with Dr. Winston and includes;

1. Passive and any active range of motions (ROM) of wrist, second and fifth MCP and PIP joints and thumb palmar and radial abduction will be measured by goniometer. Spasticity will be measured based on Modified Ashworth Scale (MAS).
2. The maximum distance between the pulp of the most flexed finger and thumb and the palm of the hand will be measured in centimeter. This distance will be measured during maximal passive extension of the fingers and thumb while the assessor keep the wrist in neutral (or as close to neutral as possible)position.
3. Intensity of pain in the wrist and hand area will be measured by NRS (numerical rating scale), for patients with sufficient cognitive capacity. In this test patients will be asked to score their pain on scale of 0 to 10. Patients who cognitively are not able to score their pian will be assessed by CNPI scale (Checklist of Nonverbal Pain Indicators). In this scale the patient will be observed at rest and during any movement and any nonverbal vocal complaints, facial grimaces, bracing, restlessness, rubbing of the affected area and verbal vocal complaints will be scored accordingly. PI will decide which one of these 2 methods is applicable, based on their assessments, patients' record and in consult with their caregivers.
4. Goal Attainment Scale (GAS): This is a patient-oriented scale to deliver the patient their desired outcomes. Up to 3 individualized, SMART (specific, measurable, achievable, realistic and timed) goals will be negotiated between participants, caregivers and their physician. At the final visit, they will be asked if they are satisfied with each of these goals and the response will be scored accordingly.

5. Hand hygiene: the evaluator will assess the patients' hands to determine the extent of palm maceration, ulceration or infection; cleanliness of the palm, ease of cleaning and nail trimming; and the effect of hygiene-related disability on other areas of functioning. This assessment is a part of disability assessment scale (DAS). The score ranges from 0 to 3 based on the severity of the maintaining the hand hygiene.
6. A review of analgesics required from patient or caregiver.
7. We will record a video while we are doing the clinical assessment. These videos will be used by Dr. Winston for training purposes. During the recording the face will be excluded with a barrier. Any other recognizable marks such as any tattoos will be blurred to maintain the privacy and security of the patients . All patients would have already had this done with their nerve blocks before the procedure. We will remind all patients not to say their names or anything that might identify them to maintain the privacy.

Statistical Analysis:

A convenience sample of n = 25 patients will be included in this study. This is consistent with existing volumes of consultations to our clinics. Study recruitment will include all patients with wrist and hand contracture that are considered for cryoneurolysis. The outcome measures that we will use are standard clinical measures, but effect sizes are not readily available from previous studies to formally calculate sample size. Furthermore, our study uses an exploratory prospective cohort design, rather than a parallel group trial design, limiting the rationale for providing a sample size calculation.

To assess for statistically significance, a paired t-test on the difference of proportions, applicable to pre-treatment and post-treatment, will be performed. We will employ repeated measures or linear mixed (multilevel) models of change to analyze within-person trajectories in all key outcomes for the intensive repeated measures data spanning the 4-month study period. Such models derive individual parameter estimates for baseline function and change pursuant to nerve or surgical procedure and will directly index the magnitude in improvement for each outcome with everyone serving as their own control (i.e., with change indexed relative to everyone's own personal baseline). If normal distribution in the outcomes does not stand, McNemar's test and

Spearman correlations will be calculated instead of paired t-test and Pearson's correlation, respectively.

The correlation between range of motion and pain score will be reviewed by Pearson's correlation and or Spearman's rank correlation at single time point. The improvement of range of motion or pain scores during two visits will be compared by two sample t test or Wilcoxon rank sum test.

Inclusion criteria:

1. Adult patients(at least 18 years old).
2. Severe claw hand with less than 4 cm distance between the pulp of the fingers and palm of the hand.
3. MAS>= 3 in wrist and hand muscles interfering with function or causing a clinical problem, due to any neurological condition.
4. Have refractory pain in wrist and hand area with no response to the usual pain management methods including oral medication or botulinum toxin injection.
5. Patients are already candidate for cryoneurolysis for pain and spasticity in their hand and wrist, based on their response to DNB.
6. Ability to attend testing sessions, comply with testing protocols and provide written informed consent. For patients who physically are not able to complete the consent process, a witness may be asked to sign and confirm their willing for participation. Legal representative may be asked to help with consent process for participants who cognitively are not able to consent on their behalf.

Exclusion Criteria:

1. Have undergone any previous peripheral nerve procedures in their affected side, for the treatment of spasticity, including previous cryoneurolysis, chemical neurolysis, neurectomy or arthroplasty.
2. Patients who received botulinum toxin in past 4 months in the same targeted muscles for cryoneurolysis, however, they may enter the study at the 4-month mark.

Recruitment:

a) Dr. Winston, as a physiatrist with expertise in neurorehabilitation of chronic neurological conditions that results in spasticity, will inform all prospective patients that

are already elected to undergo DNB and cryoneurolysis to advise them that the study is being conducted. With permission, patients or their legal representative will be contacted by the research assistant. The consent form will be offered to the patients when they are offered and selected to undergo a cryoneurolysis. The legal representative will be asked to help with consent process in participants who are physically or cognitively unable to consent. They can either consent at the time of first treatment or at their preference they will have several weeks to review and consider the desire to participate.

b) Recruitment of participants will be through spasticity clinic at Victoria General Hospital, where Dr. Winston offers DNB and cryoneurolysis to the patients, routinely, as a part of their standard care to manage pain and spasticity. As a member within the circle of care, he will approach participants regarding obtaining permission for RAs to initiate contact, as per above.
c) Prospective participants will be identified as per the point above.
d) Many of the patients are expected to come from Long Term Care Facilities. We will contact the facility to see if it is easier for our team to do an in facility follow up rather than arranging transport.

References:

1-Clavet H, Hébert PC, Fergusson D, Doucette S, Trudel G. Joint contracture following prolonged stay in the intensive care unit. CMAJ. 2008 Mar 11;178(6):691-7. doi: 10.1503/cmaj.071056. PMID: 18332384; PMCID: PMC2263098.
2- Skalsky AJ, McDonald CM. Prevention and management of limb contractures in neuromuscular diseases. Phys Med Rehabil Clin N Am. 2012 Aug;23(3):675-87. doi: 10.1016/j.pmr.2012.06.009. PMID: 22938881; PMCID: PMC3482407.
3-Diong J, Harvey LA, Kwah LK, Eyles J, Ling MJ, Ben M, Herbert RD. Incidence and predictors of contracture after spinal cord injury--a prospective cohort study. Spinal Cord. 2012 Aug;50(8):579-84. doi: 10.1038/sc.2012.25. Epub 2012 Mar 27. PMID: 22450888.
4-Matozinho CVO, Teixeira-Salmela LF, Samora GAR, Sant'Anna R, Faria CDCM, Scianni A. Incidence and potential predictors of early onset of upper-limb contractures after stroke. Disabil Rehabil. 2021 Mar;43(5):678-684. doi: 10.1080/09638288.2019.1637949. Epub 2019 Jul 22. PMID: 31328966.

5- Kwah LK, Harvey LA, Diong JHL, Herbert RD. Half of the adults who present to hospital with stroke develop at least one contracture within six months: An observational study. J Physiother. 2012;58(1):41-47. doi:10.1016/S1836-9553(12)70071-1
6-Wagner LM, Capezuti E, Brush BL, Clevenger C, Boltz M, Renz S. Contractures in Frail Nursing Home Residents. Geriatr Nurs (Minneap). 2008;29(4):259-266. doi:10.1016/J.GERINURSE.2007.09.002
7-Offenbächer M, Sauer S, Rieß J, et al. Contractures with special reference in elderly: Definition and risk factors-a systematic review with practical implications. Disabil Rehabil. 2014;36(7):529-538. doi:10.3109/09638288.2013.800596
8- Dehail P, Simon O, Godard AL, et al. Acquired deforming hypertonia and contractures in elderly subjects: Definition and prevalence in geriatric institutions (ADH survey). Ann Phys Rehabil Med. 2014;57(1):11-23. doi:10.1016/j.rehab.2013.11.001
9-Schnitzler A, Diebold A, Parratte B, Tliba L, Genêt F, Denormandie P. An alternative treatment for contractures of the elderly institutionalized persons: Microinvasive percutaneous needle tenotomy of the finger flexors. Ann Phys Rehabil Med. 2016 Apr;59(2):83-6. doi: 10.1016/j.rehab.2015.11.005. Epub 2016 Jan 13. PMID: 26797076
10-Winston P, Mills PB, Reebye R, Vincent D. Cryoneurotomy as a percutaneous mini-invasive therapy for the treatment of the spastic Limb: case presentation, review of the literature and proposed approach for use. Arch Rehabil Res Clin Transl. 2019;1(3):1-7. doi:10.1016/j.arrct.2019.100030
11-Scobie J, Winston P. Case Report: Perspective of a Caregiver on Functional Outcomes Following Bilateral Lateral Pectoral Nerve Cryoneurotomy to Treat Spasticity in a Pediatric Patient With Cerebral Palsy. Front Rehabil Sci. 2021;2:5. doi:10.3389/FRESC.2021.719054
12-Rubenstein J, Harvey AW, Vincent D, Winston P. Cryoneurotomy to reduce spasticity and improve range of motion in spastic flexed elbow. A visual vignette. Am J Phys Med Rehabil. 2020;100(5):e65. doi:10.1097/phm.0000000000001624
13-Boissonnault, Eve, Hashemi M, MacRae F, Winston P. Cryoneurolysis for the upper extremity in cerebral palsy. A novel percutaneous minimally invasive therapy for the treatment of the spastic limb. In: Coroian F, Chaleat-Valayer E, Coulet B, Laffont I, eds. Membre Supérieur Du Paralysé Cérébrale de l'enfant à l'adulte. Montpellier, France: Sauramps Medical; 2022:88-95.
14-Yelnik AP, Hentzen C, Cuvillon P, et al. French clinical guidelines for peripheral motor nerve blocks in a PRM setting. *Ann Phys Rehabil Med*. June 2019. doi:10.1016/j.rehab.2019.06.001

15-Racz GB, Noe CE, eds. *Techniques of Neurolysis*. Cham: Springer International Publishing; 2016. doi:10.1007/978-3-319-27607-6
16-Trescot AM. Cryoanalgesia in interventional pain management. *Pain Physician*. 2003;6(3):345-360. http://www.ncbi.nlm.nih.gov/pubmed/16880882. Accessed February 9, 2019.
17-Ilfeld BM, Gabriel RA, Trescot AM. Ultrasound-guided percutaneous cryoneurolysis for treatment of acute pain: could cryoanalgesia replace continuous peripheral nerve blocks? *Br J Anaesth*. 2017;119(4):709-712. doi:10.1093/bja/aex142
18-Ilfeld BM, Preciado J, Trescot AM. Novel cryoneurolysis device for the treatment of sensory and motor peripheral nerves. *Expert Rev Med Devices*. 2016;13(8):713-725. doi:10.1080/17434440.2016.1204229