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Research Paper

Human Recombinant Hyaluronidase Injections For Upper Limb Muscle Stiffness in Individuals With Cerebral Injury: A Case Series

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ABSTRACT

Spasticity, muscle stiffness and contracture cause severe disability after central nervous system injury. However, current treatment options for spasticity produce muscle weakness which can impede movement, and do not directly address muscle stiffness. Here we propose that the accumulation of hyaluronan within muscles promotes the development of muscle stiffness, and report that treatment with the enzyme hyaluronidase increases upper limb movement and reduces muscle stiffness without producing weakness. 20 patients with unilateral upper limb spasticity received multiple intramuscular injections of human recombinant hyaluronidase with saline at a single visit. The safety and efficacy of the injections, passive and active movement, and muscle stiffness at eight upper limb joints were assessed at four time points: pre-injection (T0), within 2 weeks (T1), within 4–6 weeks (T2), and within 3–5 months post-injection (T3). There were no clinically significant adverse effects from the injections. Passive movement at all joints, and active movement at most joints increased at T1, and persisted at T2 and T3 for most joints. The modified Ashworth scores also declined significantly over time post-injection. Hyaluronidase injections offer a safe and potentially efficacious treatment for muscle stiffness in neurologically impaired individuals. These results warrant confirmation in placebo-controlled clinical trials.

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1. Introduction

Spasticity is a common movement disorder after neurologic injury of cerebral and spinal origin such as stroke, traumatic brain injury, brain tumor, cerebral palsy, spinal cord injury, and multiple sclerosis. Upper limb spasticity is associated with reduced functional independence and a four-fold increase in direct care costs during the first year post-stroke alone (Lundstrom et al., 2010). The prevalence of spasticity increases over time, contributing to further disability long after the neurologic injury (Lundstrom et al., 2008). Spasticity is challenging to treat because the underlying neural and non-neural mechanisms and their interactions are not fully understood.

The neural mechanism underlying spasticity is hyper-excitability of the stretch reflex due to disinhibition of cortical influences on spinal cord circuitry, which results in velocity-dependent increase in tonic stretch reflexes (Lance, 1980). However, many patients with spasticity do not show any signs of hyperreflexia (Sinkjaer and Magnussen, 1994). Instead, muscle stiffness, defined here as increased resistance to passive movement, is the most common presenting sign in individuals with spasticity (Sheean and McGuire, 2009). Muscle stiffness adds further insult to the underlying weakness. It both prevents full passive movement (leading to abnormal posturing that can become fixed over time) and makes active movement more difficult in patients who are already weak from the neurologic injury. Non-neural peripheral mechanisms are thought to cause muscle stiffness (Burke et al., 2013; Stecco et al., 2014), although this has not been shown conclusively.

Current treatment options for spasticity include oral medications such as benzodiazepines, baclofen, and tizanidine that are central nervous system depressants used to suppress spinal hyper-excitability, and local injections of botulinum toxin used to suppress muscle overactivity. Whereas the oral medications can produce cognitive deficits, fatigue, and muscle weakness, botulinum toxin injections produce focal muscle weakness (Phadke et al., 2015). It is thus necessary to carefully balance the risks and benefits of treatment, which often remains inadequate. Furthermore, these treatments do not directly address muscle stiffness.

Here, we propose the Hyaluronan Hypothesis, which postulates that the accumulation of hyaluronan within muscles promotes the development of muscle stiffness. We report that the enzyme hyaluronidase,

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which hydrolyzes hyaluronan, and is available for off-label clinical use, increases both passive and active joint movement, and reduces muscle stiffness in individuals with upper limb spasticity. These results fill a critical gap in the understanding of muscle stiffness, and present a promising treatment for a vexing and widespread problem.

1.1. The Hyaluronan Hypothesis

Paralysis and immobility from central nervous system injury leads to rapid atrophy of muscle fibers (Springer et al., 2014), with a relative increase in the proportion of extracellular matrix, particularly in the perimysium surrounding the neurovascular tissues (de Bruin et al., 2014). Hyaluronan, a non-sulfated high molecular weight glycosaminoglycan, is particularly abundant around the endomysium, perimysium and epimysium of muscles (Piehl-Aulin et al., 1985; Laurent et al., 1991), where it provides lubrication to facilitate sliding and myofascial force transmission within and between muscles (Huijing and Jaspers, 2005). The concentration of hyaluronan can increase in serum, due to increased production after cerebral injury (Al'Qteishat et al., 2006), and in muscles from immobility (Okita et al., 2004), due to increased production, and/or decreased degradation (Jenkins et al., 2004). At high concentrations, hyaluronan itself, as well as protein-crosslinked networks or fibrillar assemblies of hyaluronan, can dramatically increase the viscoelasticity of the extracellular matrix (Matteini et al., 2009; Cowman et al., 2015); this decreases sliding of muscle fibers and reduces force transmission (Purslow, 2010), leading to muscle shortening.

The shortening may predominate in muscles with large myofascial expansions (Stecco, 2015) such as the pectoralis major, the biceps brachii, and pronator teres, connecting them together and leading to posturing of the upper limb in a typical flexor synergy pattern characterized by shoulder internal rotation, elbow flexion, and forearm pronation. Untreated and unchecked, this abnormal chronic posturing can lead to fibrosis and contracture. In fact, the accumulation of hyaluronan signals fibrosis (Jenkins et al., 2004). The aggregation of hyaluronan can disturb the balance of forces between the agonist and antagonist muscles leading to co-contraction, muscle fatigue, and excessive torques during movement (Hufschmidt and Mauritz, 1985). Thus the Hyaluronan Hypothesis provides a biomechanical explanation of how non-neural factors contribute to the development of muscle stiffness.

To test the Hyaluronan Hypothesis, we used the enzyme hyaluronidase to hydrolyze hyaluronan, reduce its molecular weight, and lower the viscosity of the extracellular matrix (Cowman et al., 2015). Hyaluronidase modifies the permeability of connective tissue through the hydrolysis of hyaluronan by splitting the glucosaminidic bond between C1 of an *N*-acetylglucosamine moiety and C4 of a glucuronic acid moiety. This temporarily decreases the viscosity of the extracellular matrix. The purpose of this case series is to describe the safety, tolerability, and preliminary efficacy of intramuscular injections of off-label human recombinant hyaluronidase-saline injections in increasing passive and active joint movement and reducing upper limb muscle stiffness in patients with cerebral injury. Human recombinant hyaluronidase has been FDA-approved since 2005 as a tissue permeability modifier. It is currently indicated as an adjuvant in subcutaneous fluid administration for achieving hydration, to increase the dispersion and absorption of other injected drugs, such as cancer chemotherapeutics, and in subcutaneous urography for improving resorption of radiopaque agents.

We present evidence that intramuscular injections of off-label human recombinant hyaluronidase offer a safe and potentially efficacious treatment for muscle stiffness that can increase passive and active joint movement, without producing weakness, in individuals with neurologic injury.

2. Methods

2.1. Patients

From May 2014 to September 2015, twenty patients (13 male and 7 female) between 10–77 years with moderately severe upper limb muscle stiffness in more than one joint, consented to and received off-label injections of recombinant hyaluronidase in combination with preservative-free normal saline, in the outpatient hand clinic at the Hospital for Joint Diseases, New York University Langone Medical Center. The patients had exhausted all available options with limited benefit, or were referred by providers seeking this specific off-label treatment. The institutional review board approved the case series (# i15-00333). All procedures were performed in accordance with the Guidelines for Good Clinical Practice as issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. The investigation and the use of patient data for research purposes were in accordance with the Declaration of the World Medical Association, and the study was performed in accordance with ethical standards on human experimentation as per the Helsinki Declaration.

The inclusion criteria for the present case series were: informed consent for the procedure and for documentation of video recordings of joint movement for clinical and academic purposes, and moderately severe muscle stiffness in more than one joint of a single upper limb defined by a modified Ashworth scale (MAS) score of ≥2. The modified Ashworth scale measures resistance to passive movement and is a common clinically used measure of muscle stiffness rather than spasticity. Exclusion criteria were severe sensory aphasia, bilateral upper limb weakness precluding compliance with a home exercise program using the unaffected limb to mobilize the affected limb, concurrent treatment of spasticity with other injectable agents such as botulinum toxin injections, and recent changes in the treatment of spasticity or underlying medical problems. Initial suitability for the injections was assessed by obtaining a history of known hypersensitivity to eggs or vaccines produced in the same manner as human recombinant hyaluronidase. The 20 cases are described in Table 1.

2.2. Injection With Human Recombinant Hyaluronidase

Hyaluronidase is supplied as a sterile, clear, colorless, non-preserved, ready-for-use solution. Each mL contains 150 USP units of recombinant human hyaluronidase with 8.5 mg sodium chloride, 1.4 mg dibasic sodium phosphate, 1 mg albumin human, 1.5 mg L-methionine, 0.2 mg polysorbate 80, and hydrochloric acid and sodium hydroxide added for pH adjustment; it has a pH of ~7.0 and an osmolality of 280–340 mOsm/kg. Given that hyaluronidase is known to be antigenic, a preliminary skin test for hypersensitivity to human recombinant hyaluronidase was performed. An intradermal injection of approximately 0.02 mL (3 units) of a 150 units/mL solution was injected. No erythema, itching, or wheal was noted in or around the injection site at 5 or 20 min in any of the patient's injected. There are no reported contraindications to intramuscular injection of hyaluronidase provided routine precautions to avoid intravascular injections are followed (Moore, 1950). The use of intramuscular procaine and hyaluronidase was previously reported for the treatment for spastic flatfoot (Locke, 1952). The dose of intramuscular hyaluronidase was determined according to each patient's pattern and extent of muscle stiffness, but the maximum dose used in this cohort was 600 IU, with no >75 IU injected into a single site. The dosage selected is well below the threshold of toxicity of hyaluronidase (Seifter, 1950).

Hylauronidase was mixed with saline in a 1:1 ratio, with 1 mL (150 IU) of hyaluronidase diluted with 1 mL of normal saline. The typical recommended dose of hyaluronidase is 150 IU. We chose to dilute it further because the modification in tissue permeability induced by the administration of hyaluronidase is influenced not only by enzyme concentration, but also by the volume and pressure of the injection

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