A Worthy – and More Accurate – Alternative to BOTOX Injections

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Skeletal muscle tissues in children and adults with neuromotor dysfunction such as cerebral palsy and stroke commonly exhibit decreased volume and increased stiffness over time. Hypertonus, defined as an increased resistance to passive stretch, can occur because of secondary non-neural changes in muscle fibers, collagen tissue, and tendon properties.[i] Viscoelasticity is a tissue property whereby the faster the change imposed on fascia-coated muscle length, the greater is the passive tension generated in the absence of evidence of muscle activation.

Hyaluronan (HA) – a.k.a. hyaluronic acid and hyaluronate – is present in a large variety of tissues and fluids including, but not limited to, connective, epithelial and neural tissues, where it delivers mechanical stability to the connective tissues while acting as a water reservoir and lubricant.[ii] HA, regarded as a biological "Jell-O", or ground substance in the extracellular matrix (ECM), facilitates muscle and fascial layer and fiber sliding and myofascial force transmission within and between muscles.

The concentration of HA – its densification - can increase in muscle and fascia after cerebral injury[iii] and with prolonged immobility.[iv] At high concentrations, "densified" HA can dramatically increase the viscoelasticity of the ECM, causing the muscle fibers and fascicles to stick to one another, reduce fiber gliding during movement and increasing stiffness.[v, vi, vii] Further densification may lead to fibrosis in the long term.[v]

The enzyme known as Hyaluronidase hydrolyzes HA, thus lowering the viscosity of the extracellular matrix fluid. It can also disrupt any densified HA aggregates or gel-like structures. Hyaluronidase -used mainly as a dispersion agent for medication - may also be useful in conditions where altered viscosity of the fascia is desired, such as in the treatment of muscle stiffness.[viii]

Raghavan et al (2016) postulate that the main contributing factor to muscle stiffness in the chronic phase after stroke is an adaptation of the muscular tissue through the accumulation of hyaluronan. They present an alternative approach to addressing the increased stiffness by releasing the restraining effects of aggregated HA on the execution of movements. They tested their hypothesis in a case series trial using injections of off-label human recombinant hyaluronidase into upper limb muscles of 18 adults at between 5 and 85 months after stroke and two school-aged children with hemiplegic cerebral palsy. The authors stated: *"In this case series, we report that intramuscular injections of the enzyme hyaluronidase increased passive and active joint movement and reduced muscle stiffness at upper limb joints in patients with spasticity of cerebral origin. The effect of treatment remained over at least three months of follow-up. These results suggest that accumulation of hyaluronan within muscles promotes the development of muscle stiffness in individuals with neurologic injury, and that intramuscular delivery of hyaluronidase is a promising direct treatment for muscle stiffness. The injections were safe and well tolerated, and without clinically significant adverse effects. Most importantly, the treatment did not pro- duce weakness, which is a common adverse effect with current treatment options for spasticity."* [ix, p. 310]

Let's keep asking attending physicians in rehabilitation medicine and pediatric orthopedics to pursue this course of science-based treatment.

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[ii] Balazs, E.A.; Laurent, T.C.; Jeanloz, R.W. Nomenclature of Hyaluronic Acid. Biochem. J. 1986, 235, 903.]

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[iv] Okita M, Yoshimura T, Nakano J, Motomura M, Eguchi K. Effects of reduced joint mobility on sarcomere length, collagen fibril arrangement in the endomysium, and hyaluronan in rat soleus muscle. J Muscle Research & Cell Motility. 2004 Apr; 25:159-66.

[v] Stecco A, Cowman M, Pirri N, Raghavan P, Pirri C. Densification: Hyaluronan Aggregation in Different Human Organs. Bioengineering. 2022 Apr 5;9(4):159.

[vi] Cowman MK, Schmidt TA, Raghavan P, Stecco A. Viscoelastic properties of hyaluronan in physiological conditions. F1000Research. 2015;4.

[vii] Matteini P, Dei L, Carretti E, et al. 2009. Structural behavior of highly concentrated hyaluronan. Biomacromolecules 10 (6), 1516–1522.

[viii] Pratt RL. Hyaluronan and the fascial frontier. International J Molecular Sci. 2021 Jun 25;22(13):6845. *KEY RESOURCE!*

[ix] Raghavan P, Lu Y, Mirchandani M, Stecco A. Human recombinant hyaluronidase injections for upper limb muscle stiffness in individuals with cerebral injury: A case series. EBioMedicine 2016; 9: 306–13.