Cross-Linked Hyaluronic Acid Injection for Neuropathic Pain

Case presentation and superficial radial nerve injection technique
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Postsurgical neuropathic pain is a frequent problem, even if the patient was in the best of hands. As with other types of nerve injury pain, postsurgical neuropathic pain is difficult to treat, usually relying on adjuvant pain medications, such as antidepressants and anticonvulsants, and nerve blocks. I have developed a treatment method that uses commercially available cross-linked hyaluronic acid (Restylane and Juvéderm) that provides prolonged, significant relief without side effects.

The first use of cross-linked hyaluronic acid to treat neuropathic pain was presented at the 2015 Annual Meeting of the American Academy of Pain Medicine [2] in National Harbor, Maryland. In the 34-month retrospective chart review, 15 neuropathic pain patients (7 women, 8 men) with 22 pain syndromes were studied. The average age of the patients was 51 years, with a mean pain duration of 66 months. The pretreatment average visual analog scale (VAS) pain score was 7.5 out of 10. After treatment, the VAS was reduced to 1.5 out of 10, and the average duration of relief was 7.7 months.

Since I presented my original work, I have treated an additional 75 patients with similar pain syndromes (ie, postherpetic neuralgia, carpal tunnel and tarsal tunnel syndrome, Bell’s Palsy tinnitus and head pain, etc). Due to the likely mechanisms of action at work, I have designated this method of treatment as Cross-Linked Neural Matrix Antinociception (XL-NMA). I present a case report of a patient with persistent neck and hand pain after undergoing cervical spine surgery.
Molecular Structure

Hyaluronic acid (HA), a proteoglycan, is a linear anionic polysaccharide\(^3\) composed of glucuronic acid and N-acetylglucosamine repeating units. It naturally occurs throughout the extracellular matrix (ECM) of the skin (56%),\(^4\) connective, epithelial, and neural tissues.\(^4,5\) Its molecular weight is 5 to 10 million Dalton (Da)\(^4\) in healthy tissues.

Cross-linked HA is an FDA-approved, commercially available cosmetic agent, which is marketed under the brand names Juvéderm\(^6\) (manufactured by Allergan, HA content 22-26 mg/mL, molecular weight 2.5 million Da)\(^6\) and Restylane\(^7\) (manufactured by Galderma, HA content 20 mg/mL, molecular weight 1 million Da).\(^8\) While the native, non-cross-linked form of HA is a liquid and metabolized in a day, the molecular cross-linking of the HA binds its individual polymeric chains and forms a viscoelastic hydrogel, accounting for its longevity (6 to 12 months) and its hygroscopic ability to absorb 1,000 times its weight in water.\(^5\)

Case Report

A 60-year-old male came to our office in April 2016 with persistent neck and bilateral hand pain after undergoing posterior cervical spine decompression at C3-C4, C4-C5, with posterior fusion, local autograft, and posterior segmental instrumentation, with lateral mass screws at C3, C4, C5. His neck injury occurred in April 2015 after a backward fall at work, when he struck his head and felt a pop in his neck.

Postoperatively, he developed increasing pain and numbness, with severe constant burning pain to the dorsa of both hands and neck (Figure 1). During anteroflexion of his neck, severe electric-like shocks radiated down his neck and spine to both upper and lower extremities. The numbness in his hands was most severe when lying on his right side.
After computed tomography (CT) myelography and radiographic (CR) testing were performed, cervical spinal segmental lesions were identified at C5-C6 and C6-C7 that would support the ongoing pain to both hands and incident, mechanical pain upon neck flexion (ie, a secondary neuropathic and myelopathic pain state and acute C6-C7 radiculopathy).

Specific lesions affected both the nerve roots bilaterally and related spinal cord segments anteriorly, which included:

- **C5-C6**: Diffuse disc osteophyte complex (bone spurs) effaced the contrast (material) anterior to the spinal cord, with effacement of the contrast surrounding each exiting C6 nerve root and expected encroachment of the exiting C6 nerves bilaterally.
C6-C7: Diffuse disc osteophyte complex effaced contrast anterior to the spinal cord, with flattening of the anterior spinal cord. Also noted was severe bilateral osseous foraminal narrowing with encroachment of both exiting C7 nerve roots.

The spine surgeon was consulted but felt there was nothing further to offer by performing another surgery.

**Treatment**

In late April 2016, the patient’s right hand was treated with Restylane (0.15 mL). The injectate was administered by placing a port with a 20-gauge needle, and then inserting a 27-gauge microcannula (DermaSculpt) with a blunt tip. To compare, the left hand was treated with a mixture of 2% plain lidocaine (2 mL) and 0.25% plain bupivacaine (4 mL). The dose per site was 1.0 to 1.5 mL. (See the sidebar [5] for a step-by-step description of this procedure.)

With some modifications, the method for injection is similar to that used for routine nerve blocks at the level of the wrist of the median nerve (MN), ulnar nerve (UN), and superficial radial nerve (SRN) at the level of the anatomical snuffbox—the triangular area of the hand formed between the thumb and second finger. Twenty-four hours after the procedure, the patient noted that digits 4 and 5 on his right hand had persistent palmar numbness but no pain, while in digits 1, 2, and 3, most of the numbness was gone but his fingertips still hurt (pain score, 4 to 5). The burning numbness in the dorsal hand had completely resolved. Overall, he felt 75% improved.

At 4 months, the patient noted his right-hand pain remained 75% to 85% improved, with a tolerable level of numbness in the lateral aspects of digits 1 and 2. There were no untoward reactions or effects. Note: Any relief from the local anesthetic administered to the left hand had resolved 1 week after the procedure, with his pain returning to baseline in that hand. Interestingly, the patient noted that although the burning numbness pain on the top of his left hand had resolved after local anesthetic injection, it was replaced by a very unpleasant, annoying sensation of numbness.

**Follow-up Treatments**

As noted, the patient reported dramatic improvement in neuropathic pain in the right hand after undergoing XL-NMA. The patient was seen again in late August 2016, when he reported that the improvement began to wane in late July 2016. He presented for augmentation XL-NMA intervention on the right hand, and XL-NMA treatment of the left hand as well as the cervicobrachial region—bilateral, proximal shoulder, C4 region, and C5-C6 level.

The patient was seen again in mid-October 2016. He reported that after the August 2016 intervention, he had ongoing and complete remission of burning pain in all pain sites. His chief complaints were a dull/sharp pain (different sensations of pain—some sharp, some dull, depending on the nerve fibers involved) to palmar and dorsal surfaces of the hand and a painful tightness around both wrists. The tightness is due to the nerve root damage in his cervical spine that involves those fibers that form all 3 main nerves of the hand (SRN, MN, and UN).

The patient noted an increase in cervical spine rotation range of motion (ROM) by 50%, as well as a 50% reduction in his cervicobrachial pain at the C5-C6 and C4 proximal shoulder regions. He presented for augmentation XL-NMA of the bilateral MN and SRN—the UN and cervicobrachial regions remained improved and were not treated.

**How It Works: Mechanisms of Action**

Table 1 outlines the proposed mechanisms of action, which are multifactorial. They are ordered with
regard to their temporal proximity to the evolving antinociception as noted over time—from the most immediate effects in the first 10 minutes after injection to the enduring and prolonged relief noted at 1 year or more in some cases.

CL-HA acts as a physical protective shield that forms a compartment that blunts the activation of spontaneous activity in the C fibers and Remak bundle afferency, as well as any aberrant nociceptive ephapse.\textsuperscript{10} Because of CL-HA’s polyanionic nature, its massive molecule (500 MDA to 100 GDa) may completely depolarize the action potential due to the size of its negative charge and prevent any transmission of the signal. The LMW/HMW mismatch correction results in TNFα-stimulated gene 6 protein modulation of the regional inflammatory response. This stabilizes and restores the immunoneural cross-talk dysregulation at the level of the extracellular neural matrix, essentially blocking what is thought to be causing the chronification of pain.\textsuperscript{11-14}

In essence, after injury or insult to the extracellular neural matrix (ECNM), an initial acute phase of overt clinical inflammation supervenes, with attendant tissue swelling and activation of Aδ and C-fiber nociceptors. However, once this becomes chronic, the tissue inflammation and immuno-neural cross-talk becomes persistent but subclinical. \textbf{Chronification} \textsuperscript{7} would occur by virtue of a re-entry, positive feedback loop, thereby sustaining and maintaining the proinflammatory, pronociceptive state, blocking entry into the healing and restoration phase (Table 2). It is self-sustaining due to a LMW/HMW-HA mismatch, likely the result of a CD44/CD168 (RHAMM) gene aberration.
Injection of CL-HA at this point results in loop interruption by correcting the LMW/HMW-HA mismatch, permitting interleukin (IL)-1β and TNFα induction of TSG-6 for inflammatory moderation, by modulation and down-regulation of the interaction between LMW-HA and CD44. This then allows for normal progression to the ECNM anti-inflammatory, antinociceptive phase, as CD44 and RHAMM (CD168) are now able to properly interact with HMW-HA. To understand this mechanism, please refer to Table 2, which illustrates the relevant cytokine cascade and neuroimmunology after ECNM injury.

The foregoing considered, CL-HA may be regarded as a super-mega Dalton form of HA. As such, it augments and sustains many times over the restorative and healing molecular biological normative functions of the body’s HMW-HA, including:

- Anti-inflammatory response
- Inhibition of scar formation
- Formation of functional super-structure aggregates
- Immunosuppression
- Antiangiogenesis
- Increased ability to bind fibrinogen for clotting
- Stimulation of peripheral blood monocytes
- Production of growth factors and matrix components

Thus, the injection of CL-HA into the ECNM may result in:
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- Interruption of this loop
- Correction of the mismatch
- Entry into the healing and restoration phase (Table 2)
- Returning the ECNM to homeostasis

**Spooky Action at a Distance Confirmed?**¹⁵

When discussing this case report with peers, I am often asked, “But how does a treatment in the periphery, well distal from the offending lesion in the neck, effect change?” In this case, the known lesions per CR and CT myelography are identified at the spinal segmental levels, C5-C6 and C6-C7 (C6 and C7 nerve roots, respectively). These lesions compromise both the nerve roots and the anterior spinal cord, which are thereby intimately part of the known root and cord derivation of the radial nerve (ie, C5, C6, C7, C8, T1). And, of course, they would support the ongoing burning pain experienced over the dorsa of both hands. However, to understand this further, one must consider the concept of deafferentation.¹⁶

**Deafferentation Pain**

Deafferentation pain is simply, “…severe spontaneous pain in body parts distal to the injury despite reduced or no sensitivity to external noxious stimuli to that body part (hypoalgesia or analgesia).”¹⁶ It may result from any injury to the nervous system, both central and peripheral, including the brain, spinal cord, and peripheral nerves. The deafferentation is believed to be due to the loss of information from the periphery to the brain. More specifically, there is an interruption in the afferent sensory information passing through the spinothalamic tract to the cortex. The domain of this tract includes the transmission of pain or nociceptive input centrally to the thalamus. Though the precise mechanism remains poorly understood, this model aptly fits the case at hand (ie, there is incomplete deafferentation of those nerve roots and spinal cord segments subserving the radial nerve).

So, applying this to the patient’s burning pain over the dorsa of the hands, in light of mechanism 3 in Table 1, an injury must occur to initiate the cytokine cascade’s proinflammatory, pronociceptive state (Table 2). This would be derived from the physical injury to the affected nerve roots and spinal cord segments. However, as the ECNM is a continuous and diffuse neuro-immunological, corporeal entity surrounding all neural structures (ie, it is one throughout), then the affected sensory neurons of the involved C6 and C7 nerve roots and spinal cord segments are in both continuous physical contact and neuro-immunological contact with those overlying the dorsum of both hands.

Hence, the injury at a distance is essentially the result of the proximal ECNM’s spooky action at a distance.¹⁵ This causes CD44, CD168 (RHAMM) to detect HAT₃, with inflammatory cytokine release of IL-1β, IL-6 and TNFα, which in due course initiates and sustains C fiber and Aδ nociceptor activation distally (Table 2, #3). With the injury of the ECNM surrounding the SRN established distally, it may now be intervened in-situ successfully with XL-NMA to achieve CL-HA LMW/HMW-HA mismatch correction and ICAM-1 (CD54) inflammatory modulation (Table 2, #3-#5 loop).

**Denouement**

Nonetheless, it is now truly gratifying to reliably obtain enduring relief of severe and intractable symptomatology with a safe and relatively minimally invasive treatment. The technique is generally simple to perform, with perhaps the most challenging aspect being the identification of the target peripheral sensory nerve, neural network, and matrix to inject. However, with standardization of techniques based on common clinical presentations, this will not be difficult.

**Summary**
I describe the use and technique of targeted SRN neural matrix antinociception injection of cross-linked hyaluronic acid in the successful treatment of neuropathic pain of the dorsum of both hands that occurred in a 60-year-old injured worker who underwent posterior cervical spine decompression. This technique has resulted in enduring relief and proved to be a safe and effective method in this patient. We recommend its routine use be considered early to manage pain in similar patients.

References:

2. Campa, JA. XL-NMA® Cross-Linked Neural Matrix Antinociception. Service Mark, Registration Number: 4899494; Registration Date: Feb 09, 2016
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