CROSS-LINKED HYALURONIC ACID - A PARADIGM SHIFT IN THE TREATMENT OF NEUROPATHIC PAIN

JOHN A. CAMPA III, MD, CLINICAL NEUROSCIENCES, ALBUQUERQUE, NEW MEXICO, USA

Statement of Problem
Persistent neuropathic pain presents a special challenge to the clinician as current treatment regimens routinely include opioids, anti-neuropathic adjuvants and nerve blocks. However, at best, only modest pain control is achieved, and they are hindered by dose limiting side effects, e.g., impaired cognition, constipation and tolerance. Hence, a method of treatment that is safe, provides prolonged, significant relief, without side effects, dose limitations, and does not affect cardiovascular stability, would be ideal.

While the literature describes the use of cross-linked hyaluronic acid (CL-HA) as a cosmetic dermal filler for soft-tissue augmentation, we believe our study is the first to assess its safety and efficacy in the treatment of neuropathic pain.

Naturally occurring HA
Hyaluronic acid (HA), a proteoglycan, is a linear, anionic, polysaccharide, composed of glucuronic acid and N-acetylglucosamine units, naturally occurring throughout the extracellular matrix of skin (56%), connective, epithelial and neural tissues. Its molecular weight is 5-10 million Daltons in healthy tissues.

Presented at: 5th World Congress on Neuropathic Pain, May 14-17, 2015, Nice, France
John A. Campa III, MD, Clinical Neurosciences · 1701 Moon St. NE - Suite 100, Albuquerque, New Mexico, USA · ph. (505) 508-1543 · fx. (505) 554-2118 · email neuropain@att.net
Cross-linked HA
Cross-linked HA commercially available and FDA approved, non-animal source, cosmetic agents are multiple, and include Juvéderm® (Allergan) HA content 22-26 mg/ml, molecular weight, 2.5 million Daltons and Restylane® (Medicis) HA content 20 mg/ml, molecular weight, 1 million Daltons. It is the cross-linking of the HA (normally a liquid, metabolized in a day) that binds its individual polymeric chains, resulting in the formation of a viscoelastic hydrogel, accounting for its longevity (6-12 mos.), and its hygroscopic ability to absorb 1000 times its weight in water.

Aim
The aim of this study is to assess the safety and efficacy of cross-linked hyaluronic acid in the treatment of neuropathic pain.

Materials & Methods
A 34 month retrospective chart review was performed, identifying 15 patients (7 female/8 male) with persistent, neuropathic pain (Table-1). The average age was 51yrs. (22-85 yrs.), with a mean pain duration of 66 mos., range, 4-200 mos. Among this group, twenty-two separate neuropathic pain syndromes were identified and initially subjected to differential local anesthetic neural blockade to determine the most reactive neural point overlying the relevant peripheral nerve innervating the painful area. Pending a positive response and after the initial anesthetic block subsided, i.e., 72 hrs. later, targeted, neural matrix antinoiception injection of CL-HA was then performed (XL-NMA™ injection method, Fig. 1-5).

Pretreatment VAS pain scores ranged from 6-10/10, with an average of 7.5/10. Note, the use of FDA approved cosmetic CL-HA agents in this study was off-label. Pain locations included: Face, 1 (5%); Spine, 6 (27%): Cervical, 1 (5%); Thoracic, 3 (14%); Lumbosacral, 2 (9%); Shoulder, 1 (5%); Elbow, 2 (9%); Wrist, 2 (9%); Thigh, 1 (5%); Feet, 9 (41%).

The injectate consisted of CL-HA agents with a fixed HA concentration of 24 mg/ml and a variable cross-linking value of 9-11%. Average dose given was 0.15 cc, range: 0.05-0.2 cc. The injection was administered either through a 27G needle, or via a variable length, atraumatic blunt-tip 27G microcannula (DermaSculpt®), after a 21G injection port was prepared. The results were assessed by the degree and duration of pain relief from a single injection.

Results
All patients injected achieved pain relief, with the average post-procedure VAS pain score being 1.5/10. The range was 0-3.5/10. The average time to achieve pain relief was 24 hrs., and the range was from 0-48 hrs. Average duration of pain relief was 7.7 mos., and ranged from 2.5-18+ months. There were no untoward reactions or effects.
**Discussion**

The aim of this study, to assess the safety and efficacy of cross-linked hyaluronic acid in the treatment of neuropathic pain, is clearly supported by the impressive results, as noted above. In particular, that all patients benefited from all perspectives, including: pain level reduction, promptness of reduction, duration of reduction and the absence of untoward reactions. Nonetheless, though the results are compelling, the mechanism or mechanisms underlying these dramatic findings requires additional study, and will likely be multifactorial in nature.

Mechanisms of primary consideration at the level of the extracellular neural matrix would include:

1) CL-HA as a physical, protective shielding and compartment: Blunting activation of spontaneous activity in C-fiber and Remak bundle afferency as well as aberrant nociceptive ephapse;

2) CL-HA anionic depolarization: Polyanionic nature results in a sustained action potential refractory state;

3) CL-HA ICAM-1 inflammatory modulation: CL-HA augmentation of the known HA intercellular adhesion molecule-1 (ICAM-1) resulting in modulation of regional, inflammatory activation - in essence, stabilizing/restoring the post-injury, immuno-neural cross-talk dysregulation at the level of the extracellular neural matrix, that resulted in the chronification of pain in the first place.

**Conclusion**

We conclude that targeted, neural sensory antinocicception injection of cross-linked hyaluronic acid is a safe and effective method of treating neuropathic pain. Its routine use should be considered early in the treatment of this patient group.

**References**


**Presented at: 5th World Congress On Neuropathic Pain, May 14-17, 2015, Nice, France**

John A. Campa III, MD, Clinical Neurosciences · 1701 Moon St. NE - Suite 100, Albuquerque, New Mexico, USA ph. (505) 508-1543 · fx. (505) 554-2118 · email neuropain@att.net
<table>
<thead>
<tr>
<th>Pt. #</th>
<th>Sex</th>
<th>Age (yrs.)</th>
<th>Pain Syndrome</th>
<th>Pain Duration</th>
<th>Relief Duration</th>
</tr>
</thead>
</table>
Fig. 1 - Reactive point neural matrix entry port targeting.
Fig. 2 - Needle insertion into neural matrix, above fascial plane.
Fig. 3 - Neural matrix CL-HA implantation.

Fig. 4 - Formation of CL-HA neural matrix protective compartmental scaffolding.
Fig. 5 - External pressure extends CL-HA shielding along neural long axis.