# Cross-Linked Hyaluronic Acid: A Paradigm Shift In The Treatment of Neuropathic Pain


## John A. Campa III, MD - Attending Neurologist

**Neuropathic Pain Center For Clinical Research & Treatment, Albuquerque, New Mexico - USA**

1701 Moon St. NE, Suite 100, Albuquerque, New Mexico, 87112 - USA · ph. (505) 508-1543 · http://paindiagnosis.net

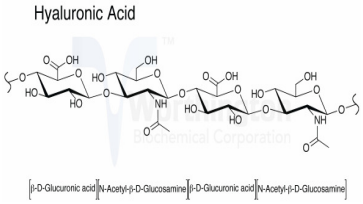

## Statement of Problem

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[1], we believe our study is the first to assess its safety and efficacy in the treatment of neuropathic pain.

### Naturally occurring (non-cross-linked) HA

Hyaluronic acid (HA), a proteoglycan, is a linear, anionic, polysaccharide[2] (below), composed of glucuronic acid and N-acetylglucosamine units, naturally occurring throughout the extracellular matrix (ECM) of the skin (56%)[3], connective, epithelial and neural tissues.[1,2] Its molecular weight is 5-10 million Daltons[3] in healthy tissues.




**Non-Cross-linked Hyaluronic acid structure[2].**

### Cross-Linked HA

Cross-linked HA commercially available and FDA approved, non-animal source, cosmetic agents are multiple, and include Juvéderm®[4] (Allergan), HA content 22-26 mg/ml, molecular weight, 2.5 million Daltons[5] and Restylane®[6] (Medicis), HA content 20 mg/ml, molecular weight, 1 million Daltons[5]. It is the cross-linking of the HA (native, non-cross-linked form is 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.[1]

## Aim

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

## Material & 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 51 yrs. (22-85 yrs.), with a mean pain duration of 66 mos., range, 4-200 mos. Among this group, 22 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[7]. Pending a positive response (≥50% VAS pain score reduction) and after the initial anesthetic block subsided, i.e., 72 hrs. later, targeted, neural matrix antinociception injection of CL-HA was then performed (XL-NMA® injection method[7], Fig. 1-3). Pretreatment VAS pain scores ranged from 6-10/10, with an average of 7.5/10.

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 20G injection port was prepared. The results were assessed by the degree and duration of pain relief from a single injection. All patients approved and consented to the use of their clinical data for this study. Note: the use of FDA approved cosmetic CL-HA agents in this study was off-label.

## 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. Average dose given was 0.15 cc, range: 0.05-0.2 cc. 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 supported by these results. All patients benefited from all perspectives: pain reduction, promptness of reduction, duration of reduction and absence of untoward reactions. Mechanisms underlying these findings are likely multifactorial and require additional study. Nonetheless, they 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[8];
2. *CL-HA anionic depolarization:* Polyanionic nature results in a sustained action potential refractory state;
3. *CL-HA ICAM-1 (Intercellular Adhesion Molecule-1) inflammatory modulation[9]:* Results in modulation of the regional, inflammatory activation, thereby stabilizing and restoring the ECM 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[10].

## References


1. Bogdan Allemann I, Baumann L. Hyaluronic acid gel preparations in the treatment of facial wrinkles and folds. Clin Interv Aging. 2008; 3(4): 629-34.

2. Atkins, E, Sheehan, J. Structure of Hyaluronic Acid. Nature New Biol. 1972; Feb 23; 235(60): 253-4.

3. Ågerup, B, Wik, O. NASHATM, The Monograph. Q-Med AB. 2008; 1-24.

4. Allergan, Inc, Juvéderm Gel, package Insert.

5. Lim L. Executive Summary Dermal Filler Devices, Public Advisory Committee Meeting. FDA. 2008; Nov 18: 1-41.

6. Medicis Aesthetics Inc, Restylane Gel, package Insert.

7. Campa, JA. Novel indication and technique for the use of cross-linked hyaluronic acid in the management of pain. Patentscope. 2014; PCT Application No. 20140349958; patent pending. https://patentscope.wipo.int/search/en/search.jsf

8. Vorvolakos, K, Isayeva, I, Do Luu, HM, Patwardhan, D, Pollack, S. Ionically cross-linked hyaluronic acid: wetting, lubrication, and viscoelasticity of a modified adhesion gel. Med Devices (Auckl). 2011; 4:1-10.

9. Chen, J, Abatangelo, G. Functions of hyaluronan in wound repair. Wound Rep Reg. 1999; 7: 79–89.

10. Tajerian, M, Clark, D. The role of the extracellular matrix in chronic pain following injury. Pain. 2015;156: 366-370.


## Conclusions

**We conclude that targeted, neural matrix antinociception 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.**

**Table-1: CL-HA Patients Treated & Pain Syndromes**

| Pt. # | Sex | Age (yr.) | Pain Syndrome | Pain Duration | Relief Duration |
|---|---|---|---|---|---|
| 1 | M | 27 | Paroxysmal LBP & Bil. buttock pain-spasm. Sciatic N. | 8 yrs. | 24 mos. |
| 2 | M | 78 | DM BLE Polyneuropathy foot pain. Tibial N. | 10 yrs. | 30+ mos. |
| 2 | M | 82 | PHN Shingles pain, Lt. ant. thigh. Ant. Femoral Cut. N. | 6 mos. | 3+ mos. |
| 3 | M | 48 | Idio. BLE Polyneuropathy foot pain. Tibial N. | 11 yrs. | 12 mos. |
| 3 | M | 48 | BLE - TTS sharp foot pain. Tibial N. | 5 yrs. | 12 mos. |
| 4 | F | 25 | Lt. Posterolat. chest wall pain, s/p crush injury. 7th ICN. | 3 yrs. | 12 mos. |
| 5 | F | 41 | Post-surg. neuritis, Lt. 5th toe. Sural Cut. N. | 4 mos. | 8 mos. |
| 6 | F | 73 | DM BLE Polyneuropathy foot pain. Tibial N. | 6 mos. | 2.5+ mos. |
| 7 | M | 55 | Lt. neck pain, C3-4, C4-5, C5-6 HNP/Cord-Root Impng. | 12 mos. | 6.5 mos. |
| 7 | M | 55 | Lt. shoulder pain, SST/Bcps td. inj. P. Supraclavicular N. | 12 mos. | 5.5 mos. |
| 8 | M | 66 | Lt. forefoot pain, DJD, digits #2, 3, MTH. Tibial N. | 20 yrs. | 12 mos. |
| 9 | F | 44 | Rt. foot post-traumatic neuritis. Sup. Peroneal N. | 3.5 yrs. | 4 mos. |
| 9 | F | 44 | Rt. LBP, SIJ osteoarthrosis+osteophyte. Sup. Cluneal N. | 7 yrs., 10 mos. | 4 mos. |
| 10 | F | 60 | Idio. BLE Polyneuropathy foot pain. Tibial N. | 10 yrs. | 24 mos. |
| 10 | F | 60 | Lt. wrist pain, scaphoid osteonecrosis. Sup. Radial N. | 6 mos. | 3.5 mos. |
| 10 | F | 60 | Rt. T6-7, T7-8 pain; Intraforaminal perineural cysts. ICN | 2 yrs., 5 mos. | 12 mos. |
| 11 | M | 45 | Lt. elbow pain, post-traumatic, MVA. Ulnar N. | 2 yrs., 8 mos. | 2.5 mos. |
| 11 | M | 45 | Lt. wrist pain, post-traumatic, MVA. Ulnar N. | 2 yrs., 8 mos. | 2.5 mos. |
| 12 | F | 45 | Fibromyalgia, T spine. ICN-Dorsal Rami, Sensory Cut. N. | 10 yrs. | 4 mos. |
| 13 | M | 27 | Post-surg. mid-face pain, Infraorbital N. | 5 yrs., 10 mos. | 4 mos. |
| 14 | M | 35 | BLE-TTS sharp foot pain. Tibial N. | 3 yrs., 10 mos. | 4.5 mos. |
| 15 | F | 42 | Rt. Lateral Epicondylitis-Tennis Elbow. Lat. Anteb. Cut. N. | 12 mos. | 14 + mos. |

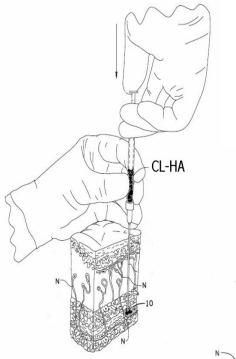



**Fig. 1 - Neural matrix CL-HA implantation.**

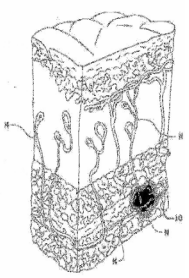


**Fig. 2 - Formation of CL-HA neural matrix protective compartmental scaffolding.**

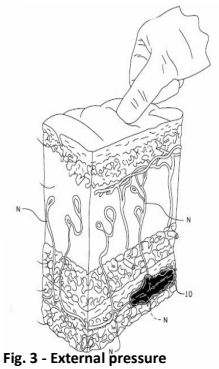


**Fig. 3 - External pressure extends CL-HA shielding along neural long axis.**

XL-NMA