Clinical Findings

HEPARIN ALLEVIATES PAIN IN NERVE ENTRAPMENTS

Wladislaw Ellis, MD

Abstract. *Given the evolving importance of glycosaminoglycans in modulating small nerve-fiber function, the author investigated the hypothesis that small dose unfractionated heparin can mitigate painful symptomatology in nerve-entrapment syndromes. Consecutive subjects with diagnoses of brachial plexus irritation/thoracic outlet syndrome (TOS), carpal tunnel syndrome, and ulnar nerve entrapment (UNE) at the elbow received six weekly localized injections of low-dose heparin. Pain scores, as measured with a visual analog scale, were recorded. An initial blinded control was performed in all subjects. In TOS, single treatments resulted in 41.8% pain alleviation, with 83.8% pain alleviation at the end of the series. Relief was generally lasting, but subjects continued to be susceptible to re-injury. The investigators found that perineural unfractionated heparin injections are a safe and effective method of pain relief in a number of nerve entrapment syndromes.*

Descriptors. *heparin, nerve entrapments, thoracic outlet syndrome*

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INTRODUCTION

Glycosaminoglycans (GAG) have been little appreciated in peripheral nerve entrapments. Their many functions include reducing collagen cross-linking, stabilizing vascular endothelium, modulating growth-factor function, and significant neuroprotection. These functions have indicated a potential therapeutic effect in disturbances characterized by neural irritability, fibrosis, and microvascular changes, such as occur in peripheral nerve entrapments (1-7,10). Although work on hyaluronic acid, dermatan sulfate, heparan, and decorin has been attracting more interest, the best-characterized GAG for human use continues to be heparin (8).

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Less than 3% of the heparin polymer is associated with anti-coagulation (9). Other effects and functions include anti-inflammation, charge stabilization, neurite differentiation, and inhibition of fibrosis (3,10-12). And, there is clinical evidence in support of heparin's use and effectiveness in asthma, adult respiratory distress syndrome (ARDS), ulcerative colitis, rheumatoid arthritis, and myocardial infarction (14); and clinically relevant efficacy has been documented in burns and radiation-induced neuropathy (15,16).

Fortunately, all of the effects of interest in nerve entrapments occur at doses that do not activate anti-coagulation to any significant extent. Since nerve entrapments show evidence of localized inflammation, endothelial dysfunction, and neural irritability, it is hypothesized that perineural infiltration of heparin could modulate painful symptoms in these entrapments. Given the author's practice, the target population was largely those

exhibiting signs of brachial plexus irritation, best characterized by Roos and termed *neurogenic TOS*, *hand/shoulder/arm syndrome*, *cervical brachial syndrome*, or *double* or *triple-crush injury*. (17-19). Pharmacotherapy with analgesics, tricyclics, NSAIDs, vaso-active agents, or nerve-membrane stabilizers most often results in little effect. Physical therapy is helpful, but too often the clinical course is one of increased symptomatology and dysfunction, leading to surgical decompression (20).

Following unexpectedly positive results in several patients with TOS, the author decided to initiate a controlled study, including small numbers of patients with other entrapments.

METHODOLOGY

Subjects. TOS can be subdivided into a number of categories. *True* or *Classical TOS* occurs with obvious bony or soft-tissue abnormalities and is accompanied with objective neurological changes. *Vascular TOS* is caused by arterial abnormalities, such as subclavian arterial post-stenotic dilatation, aneurysms, venous thrombi, or other obstructions. Both of these (classical and vascular) total approximately 1-3% of individuals presenting with typical symptoms of pain and paresthesias in the shoulder and arm, provoked by brachial plexus compression, and other findings of brachial plexus irritation.

The third category is that of *Disputed* or *Neurogenic TOS*. This is defined by the absence of structural or vascular abnormalities in the presence of symptomatology. Given that the vast majority of patients fall into this category and that the pathophysiologies of these categories differ, the author elected to restrict all subjects in this study with TOS to just this category.

All subjects were initially referred by other specialists for further evaluation and treatment secondary to suspected nerve entrapments. Twenty-four consecutive subjects with symptoms and findings of TOS, who satisfied the enrollment criteria, were enrolled. The median age was 39.1 years (SD 9.6), with a 5:1 female/male ratio. Mean symptom duration was 31.3 months (SD 25.0).

A homogenous TOS population of subjects with TOS was defined by applying various inclusion and exclusion criteria.

Inclusion critera. Inclusion criteria were: repetitive work-related onset; paresthesias and pain occurring distally in the hand and then progressing proximally to involve the elbow, shoulder, neck, head, parascapular area, and anterior chest wall; increased symptoms with use; increased symptoms on stretching of the brachial plexus (positive Roos' surrender test and positive brachial plexus traction test); pain and symptom augmentation on manual pressure over the brachial plexus; hypo- or hyperesthesia; supraclavicular swelling; trapezial spasm; and swelling in the distal extremities following increased symptomatology.

Exclusion criteria. Exclusion criteria were: systemic diseases (hormonal, malignant, rheumatic, coagulative, or vasoactive); electrodiagnostic evidence of impairment at the wrist or elbow; bony abnormalities such as cervical ribs, abnormally angulated clavicle, symmetrical or subluxated first rib; orthopedic malformations or disease of the shoulder, arm or spine; any evidence of consistent venous or arterial impingement on the brachial plexus; and any evidence or history of surgical interventions to the brachial plexus, spine, clavicle, shoulder or arm.

Other considerations. Further study utilizing electrodiagnostics and magnetic resonance imaging of both the brachial plexus, shoulder, and cervical spine gave no indication of abnormalities. Three subjects with clinical and electrophysiological findings, consistent with carpal tunnel syndrome, aged 34, 35, and 41 (all female), and symptom durations averaging 6.5 months were included. Three subjects with clinical findings of UNE at the elbow, aged 31, 36 and 43, (all female) with symptom durations averaging 9 months were also included.

All subjects were either stable or worsening symptomatically at the time of inclusion despite at least two months of appropriate physical therapy. Use of all pharmacological substances was stable for at least two months and remained constant throughout the experimental period.

PROCEDURE

In the informed consent and verbally, all subjects were told that they would receive seven weekly injections of either a placebo or an active ingredient and were asked to keep a daily record of the location and intensity of their symptoms. The placebo chosen was equal volume 2% procaine, since normal saline proved to be an irritant. Pre-study treatment of eleven other subjects with TOS, with four consecutive weekly injections supraclavicularly using procaine, showed no symptom changes.

Patients with TOS received two separate injections of 0.5 ml each of unfractionated heparin, 2,000 units buffered to a pH of 7 at sites intended to bracket the upper and lower roots of the plexus, in the interscalene compartment. Injections were performed perpendicular to the skin at the lateral border of the sternocleidomastoid where it angulates and forms a hollow with the anterior edge of the trapezius for the upper roots. The second infiltration occurred immediately lateral to the body of the anterior scalene, roughly 3 cm superior to the clavicle and 7-10 cm lateral to the mid-line for the lower roots. Depth was determined by slowly advancing a 1 ", 25-gauge needle-syringe with positive plunger pressure until paresthesias or burning/lancinating pain was obtained, then withdrawing 2 mm. In carpal tunnel syndrome, the same volume was injected in a similar manner at the wrist crease immediately lateral to the flexor carpi ulnaris tendon. Subjects with UNE received a similar injection immediately proximal to the ulnar groove at the site of maximal nerve tenderness.

PAIN ASSESSMENT

The intensity of pain was determined using an analog pain scale (APS) with scoring obtained immediately prior to treatment; 1 hour subsequent to treatment; 24 hours and 72 hours following treatment (21). Subjects were blinded to control injections, which were administered during the first experimental session and contained 0.5 ml of 2% procaine injected in a manner identical to the experimental injections.

Heparin has well-recognized side effects; and complete blood counts, serum electrolytes, serum enzymes, coagulation time, and partial thromboplastin times were obtained prior to treatment, at week-three, and following completion of the protocol (22,23).

RESULTS

Control group. The initial average APS reading was 6.07 ± 1.58 ($p < 0.001$). Controlled treatment showed little change in APS (Table I). Previous results showed no cumulative effects with multiple treatments using procaine.

Treatment group. The initial APS reading was 6.24 ± 1.60 in the TOS subjects. These patients showed 4% worsening at 1 hour, 31.7% improvement at 24 hours, and 41.8% improvement (APS 3.6 ± 1.5 $p < 0.001$) at 72 hours following the first experimental treatment with heparin (Table I).

Follow-up. Six subsequent weekly experimental treatments resulted in a cumulative reduction in painful symptomatology in a stepwise fashion. At the end of the protocol, there was an average of 83.8% (APS 0.98±0.87 $p < 0.0001$) decrease in pain. Five subjects become symptom-free with less than six treatments. Seven subjects (34%) were symptom-free at the end of the protocol (Table II). Clinical testing prior to each injection revealed no change following the control, and then a progressive increase in range of motion on brachial plexus traction testing and less pain and paresthesias on pressure administered supraclavicularly.

Two of three subjects with carpal tunnel syndrome had progressive diminution of symptoms with one becoming symptom-free after three treatments and the other having no painful symptoms, but continued paresthesias after six treatments. The third subject showed no response after three treatments and elected to discontinue.

Of the three subjects with UNE, one became symptom-free after five treatments. The two other subjects had progressive improvement with 91% relief in one and

had progressive improvement with 91% relief in one and 65% in the other after six treatments.

All subjects reported frequent aching sensation at the point of injection for up to one day following treatment. No adverse reactions were noted. All serum, electrolyte, and hemostatic functions remained within normal limits.

In the majority of subjects, symptom relief peaked at three days post-treatment and then slowly increased with subsequent treatments in stepwise fashion, reaching a relative plateau during treatments #5 and #6. This was documented by APS measurements out to 72 hours and by review of the patients' daily records prior to each subsequent injection and at the end of the protocol. Three-month follow-up showed that symptom improvement remained stable as long as the subjects were not reinjured.

Heparin can dramatically reduce painful symptoms; however, the subjects continued to be vulnerable to easy reinjury following predictable activities such as keyboard use, writing, hairdressing, dishwashing, or yard work. Prolonged moderate vibration (such as that which occurs during automobile trips or public transport) or sudden physical effort also provoked a return of symptoms, often with a delay time of 6-24 hours. This was more of a problem in subjects with complete relief as they would forget their limitations. Such reinjuries were well controlled with further treatment. Previously disabled workers were returned to modified duties, needing occasional further treatment when reinjured.

DISCUSSION

Heparin provides a novel, effective, and safe means for controlling symptoms in mild to moderate entrapments of the upper extremity. A single treatment resulted in average pain reduction of 41.8% at three days. Six or fewer weekly treatments resulted in an overall improvement of 83.8% in TOS; 66% in carpal tunnel syndrome; and 85% in UNE, the sample size being small in the latter two disorders. Although injections for TOS were restricted to the interscalene compartment, similar results can be expected with entrapments at the pectoralis minor insertion and paravertebrally.

Although the majority of the observations and results were found in humans suffering from carpal tunnel syndrome, the author opines that the intraoperatively ob-

Table I. Analog pain scores of TOS patients heparin-treated and untreated.

	Prior to treatment APS ± SD	1 hour post-treatment APS ± SD	24 hours post-treatment APS ± SD	72 hours post-treatment APS ± SD
Heparin treated N = 24	6.24 ± 1.60	6.44 ± 1.71	4.26 ± 1.69	3.63 ± 1.43*
Control (2% procaine) N = 24	6.07 ± 1.58	6.33 ± 1.73	5.95 ± 1.59	6.01 ± 1.60

APS = analog pain scale score
* $p < 0.001$

Table II. Analog pain scale readings 72 hours following sequential heparin treatments.

Prior to treatment	1 treatment	2 treatments	3 treatments	4 treatments	5 treatments	6 treatments
6.2 ± 1.6 N = 24	3.6 ± 1.4 p < 0.0001 N = 24	2.7 ± 1.4 p < 0.0001 N = 24	2.3 ± 1.3 p < 0.0001 N = 24	1.8 ± 1.2 p < 0.0001 N = 23	1.8 ± 1.6 p < 0.0001 N = 22	1.5 ± 1.3 p < 0.0001 N = 19

served edema and perineural fibrosis during brachial plexus decompression gives them credence as a more general phenomenon.

The pathophysiology of brachial plexus and other entrapments is probably initiated by a progressive sclerosis occurring endoneurally caused by ischemia of the vasa nervorum (24,25). Whether directly traumatic or due to inappropriate compression from other sources, this ischemia can lead to endothelial dysfunction (26,27). The consequent plasma and platelet extravasation produce an endoneurial edema which, in effect, becomes a compartment syndrome containing the significantly increased internal pressure by a fairly rigid nerve sheath (28). This intraneural edema recruits leukocytes, macrophages, and mast cells producing inflammatory symptoms. The consequent combination of edema, cytokines, and growth factors significantly alters the endoneurial and epineurial extracellular matrix promoting collagen deposition, further restricting the endoneurial space.

It is highly likely that the analgetic relief due to unfractionated heparin is produced by stabilization of the microvascular endothelium, stabilization of localized mast cells and monocyte/macrophages, the sequestration and inhibition of inflammatory cytokines, and electrical-charge stabilization.

These results and putative mechanisms indicate that the extracellular matrix is important in regulating the pathologies produced in entrapments and possibly neuropathic pain generally, and that glycosaminoglycans can be a significant factor in the homeostasis of the neural environment. Ischemia, with its consequence of edema and perineural infiltration, is an important generator of these symptoms, and, although the micro-environment can be manipulated with significant or complete symptom reduction of neuropathic symptomatology, a structural residue remains that perpetuates hypersensitivity to reinjury.

As a consequence, this traumatized nerve becomes vulnerable to repeated bouts of further ischemia in the vasa nervorum precipitated by inappropriate movements or static positions that stretch the nerve. This vicious cycle of repeated micro-inflammation progressively involves more neural fascicles, thus spreading symptoms, and promotes neurite outgrowths and an evolving perineural and endoneurial fibrosis as documented by perineural fibrotic tissue taken surgically during decompressions (personal observations made on perineural fibrotic samples taken intraoperatively during decompressions and analyzed by L Kruger - UCLA and P Geppetti - UCSF). This fibrotic tissue has been found to have a high concentration of small myelinated and unmyelinated fibers which are reactive to substance P and calcitonin gene-related protein (29,30). Given the lack of any literature documenting these observations, the author is attempting to obtain more samples of perineural fibrosis in painful entrapments. The attendant scalene muscle hypertrophy and muscle-type transformation noted by the author and others is possibly caused by the inflammatory growth factors and activated small nerve fibers (31).

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