Rationale for Axillary Nerve Stimulation for Post-Stroke Shoulder Pain

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BACKGROUND

Post-Stroke Shoulder Pain (PSSP) or Hemiplegic Shoulder Pain (HSP) is a common and lasting impairment after stroke with incidence ranging from 30% – 70%.[1,2] Additionally, a strong association of HSP with decreases in quality of life have been established which signals that more focus on screening and treatment is required.[3] The post-stroke shoulder has a multitude of impairments not limited to pain. These factors often lead to non-use and because most upper limb activities are initiated at the shoulder, upper limb function or Activities of Daily Living (ADL's) such as getting dressed, eating, or even using the limb as an assist to the unimpaired extremity are limited. Intervention for HSP is largely focused on prevention, compensatory techniques, and symptom management such as taping, slinging, and pain medications (oral and injected), and has only shown marginal benefit.[1,4-7]

Clearly solutions are needed that address the underlying pain mechanisms, impaired shoulder mechanics, and motor recovery opportunity in this large population of underserved patients. The objective of this review is to focus on a novel implantable solution, the StimRouter™. Its simple, effective design and low risk implantation procedure make it well-suited for deployment within the rehabilitation environment.

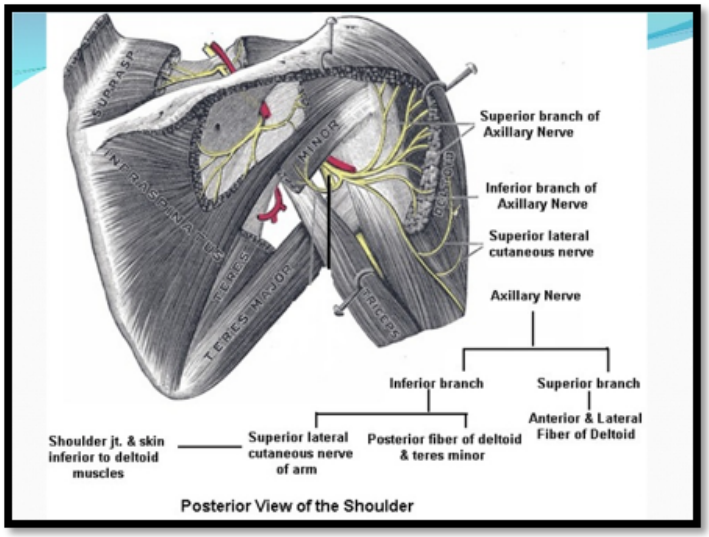
THE PAINFUL POST-STROKE SHOULDER

The painful post-stroke shoulder is most likely multifactorial in terms of mechanism, e.g; peripheral versus central, nociceptive versus neuropathic, as cases can be made and evidence will support contribution from any or all of these in a given presentation.[8-10] Post-stroke shoulder subluxation (partial dislocation) and pain are often used interchangeably and arguably incoherently as the correlation is modest at best. Therefore, it is prudent to separate these two impairments as we examine mechanisms and interventions.[11]

Starting with a direct Central Nervous System (CNS) injury, accompanying paralysis, spasticity, sensory impairment/ dysfunction, subsequent joint malalignment, disuse (central and peripheral), local tissue changes, altered feedback loops, and peripheral nerve changes, it becomes clear that the etiology of HSP is complicated and comprehensive. From a differential diagnoses perspective, there may be ways to shorten or weight the list e.g. stroke location, pain type/distribution/pattern, nerve blocks, nerve conduction testing, imaging…but singling out a primary mechanism could prove to be elusive and given the limited solutions may not lead to a better outcome.

NERVOUS SYSTEM INVOLVEMENT

Starting with an initial CNS insult via a Stroke or Traumatic Brain injury (TBI), a central mechanism for pain exists. Not to be confused with central sensitization, the "central drivers" of central neuropathic pain are often accompanied by clinical symptoms and regional distribution e.g. burning, prickling, tingling, stabbing, shooting, tightness, and coldness.[12] These symptoms are not exclusive to central pain and often are challenging to differentially diagnose with the presence of other sensory deficits following a stroke and the sequelae of peripheral impairments that often follow a CNS insult. In stroke, the location of insult with either direct thalamic or indirect spinothalamic pathway involvement, e.g. Wallenberg Syndrome with contralateral body symptoms increased the likelihood of central mechanism, i.e. Central Post Stroke Pain (CPSP). As the aforementioned neuropathic symptoms and others such as allodynia or hyperalgesia also apply to peripheral neuropathies, the presence of symptoms in body segment, such as the shoulder, alone is not enough for a differential diagnoses (central versus peripheral).[12]



Examining the peripheral nervous system's contribution to HSP opens up several potential means of involvement. The glenohumeral (GH) joint is innervated by articular branches of the axillary, suprascapular, lateral pectoral, and possibly sympathetic ganglia nerve branches.[13] While being candidates for peripheral pain transmission back to the CNS, the same nerves also have a descending motor component around the shoulder. With altered mechanics (weakness/spasticity) and subsequent malalignment around the shoulder, these nerves can also experience direct trauma.[14] The axillary nerve is arguably most susceptible to this trauma given it proximity and path around the GH joint. Constituting peripheral mononeuropathic pain, the symptom distribution would be suspected to be more localized.

Central Sensitization (CS) and autonomic nervous system involvement can also be included in the discussion of HSP. With CS, chronic peripheral deficits/pain and nervous system input (or lack there-of) can lead to adaptation or disinhibition of the nervous system and can be positioned as a mechanism, mediator, and part of the symptomology of HSP.[7] Clearly, nervous system impairment and adaptation as

a combination of the direct CNS insult and of the multitude of altered or damaged peripheral nervous system inputs create a test for clinicians to pinpoint causation in these patients and subsequently make treatment choices challenging.

MUSCULOSKELETAL INVOLVEMENT

While described as a ball and socket joint, the GH joint has a very shallow "socket," and gliding/translation is part of normal mechanics for most shoulder movements. The complex interaction of the rotator cuff muscles and primary movers of a healthy shoulder provide a balance of stability/compression with rotary motion of the GH joint and the scapula-thoracic joint.

Outside the context of stroke, shoulder dysfunction and pain related to musculoskeletal imbalance, weakness, contracture, and injury are commonplace. Impingement, rotator cuff tears, dislocation, frozen shoulder, among others are prevalent in the general population with "intact" nervous systems to control movement. It is logical to suggest that impairment to the control and activation of these muscles after a stroke or brain injury will lead to mechanical misalignment at a minimum.

Following a stroke and subsequent paralysis of the upper limb immediately places the joint at risk. Given that it is largely in a gravity-dependent position, the lack of tone in the muscles surrounding the joint place the "approximation" of the GH joint onto non-contractile elements such as the joint capsule and ligaments. Forgiving by nature, these structures will quickly yield to the weight of the limb and evidence of subluxation can be seen acutely following a stroke. As motor recovery begins, so does spasticity and any volition movements from recovery or less impaired muscles along with non-volitional contribution from spasticity will occur across a delicate joint that is almost certainly misaligned. The direct and indirect consequences of this sequela, as they relate to pain, are obvious and multi-fold.

TREATMENT WITH NEUROMODULATION

The concept of using Electrical Stimulation (ES) on the post-stroke shoulder is not new. The modality of ES has characteristics that can potentially address and have mechanism to improve many of the factors of PSSP/HSP. Starting with peripheral excitation of sensory and motor nerves and accompanying direct and indirect CNS input along with increased blood flow, improved mechanical alignment, and potential reduction in spasticity create a widespread effect on the multiple mechanisms of pain. The earliest successful efforts with Neuromodulation were with surface stimulation.

There have been many published reports on using single channel surface stimulation effectively to manage PSSP as well as subluxation.[5,15-20] The single channel was customarily placed on the posterior or middle deltoid and upper trapezius muscle. The target of the trapezius placement was the deeper muscles of the rotator cuff, specifically the supraspinatus, but if motor response was elicited the upper trapezius was first to activate. Given that the upper trapezius does not cross the GH joint and often creates an uncomfortable local response, the stimulation limits were often dictated by this placement. Other mixes of placement evolved and additional channels were added, but even the conventional one channel approach yielded very good results. Despite good outcomes, the challenges of surface stimulation with comfort, reproducibility, ease of use, lack of localization or specific control… have limited the widespread use of the surface neuromuscular electrical stimulation approach to this problem.[20-22]

Recent advancements in neuromodulation have been through various techniques with partially implanted (percutaneous) or fully implanted devices. Results from these trials show promising results and address many of the limitations of pure surface stimulation although arguably creating others with their technologies e.g. percutaneous lead. The research has evolved over the last decade and much has been learned on targeting the stimulation both in terms of implant location and stimulation characteristics for pain management specific to the hemiplegic shoulder, i.e., sensory versus motor.

The main neuromodulation driver for pain relief in HSP, sensory vs. motor, is a dynamic topic without a clear winner. There are many theories on the sensory mechanisms outside of gate theory as it applies to stroke and the additional central component not seen in our traditional pain patients., e.g. resetting; desensitization, etc. Motor level stimulation has been reported to target the central or regional pain patterning with sympathetic involvement as well as peripheral mechanisms. **The debate centers on the question "Is direct stimulation input combined with the additional "indirect" afferent input that results from motor level stimulation the ideal driver for central desensitization in HSP?"** The direct and indirect benefits of motor-level stimulation for HSP appear to be an additional value from just a pure sensory (gate theory) and accompanying indirect actions.[21] However, given the faulty alignment that is commonly present in HSP, any motor activity should be positively addressing the pathokinesiology of the joint. Moreover, the muscles selected to recruit should facilitate a better posture for the GH joint in the context of the individual.

Neuromodulations unique and "tunable" mechanism of action has a potential pathway to influence the multitude of mechanistic players in HSP. Regardless of proposed primary driver of pain, the local impact of neuromodulation of HSP warrants consideration.[23] Implementing neuromodulation with an understanding of the direct and indirect electrophysiological effects will likely result in more tailored treatment within the modality as the technology evolves.

THE STIMROUTER™

One recently FDA cleared device for chronic peripheral nerve pain is the StimRouter (Bioness, Valencia CA), a small implantable lead powered by a wireless patch, the External

Pulse Transmitter (EPT), worn on the skin surface (Figure 1). StimRouter incorporates “Electrical Field Induction” via a wearable technology that externally generates an electrical field that is captured by the receiver of the lead just under the skin and transmits it to the electrodes at the lead tip millimeters away from the peripheral nerve. The Peripheral Nerve Stimulator (PNS) can be programmed by a clinician and the patient can control their customized programs and intensities through a wireless hand-held remote.

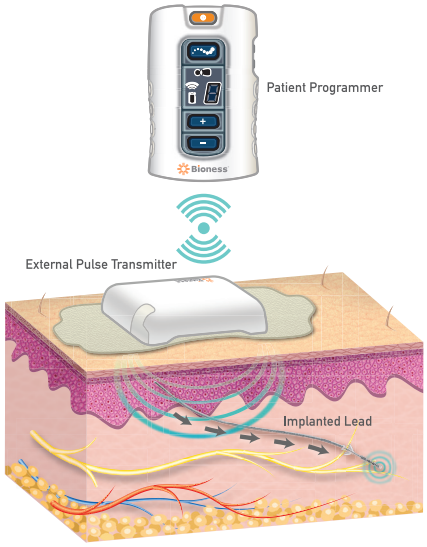


Figure 1

There are no implanted batteries to replace or recharge and the small, 15cm lead itself is implanted via an injection-like approach with local anesthesia and a small incision. Daily management involves placing the wearable over the lead pickup via an adhesive patch and activating the system with the wireless remote. Dosage levels and duration are stored in the EPT unit and can be accessed by the clinician during follow-up.

In a multi-center randomized clinical trial, the StimRouter was studied to compare peripheral nerve stimulation to “normal therapy” on 18 different peripheral nerves. Subjects (n=94) with chronic peripheral pain in the upper extremity, lower extremity or trunk, were implanted with the StimRouter and randomized to a treatment (active stimulation) or control group (sham stimulation). At 3-months the group receiving StimRouter treatment demonstrated a statistically significant improvement in pain as compared to the control group ($p<0.0001$). Following the 3-months of sham stimulation, subjects in the control group crossed-over to receive active treatment for 3-months; those that did demonstrated a statistically significant improvement in pain relief compared to baseline. No serious adverse events related to the device were reported during the duration of the study (12-months). Additionally, subjects using the StimRouter showed more favorable outcomes related to quality of life and satisfaction as compared to those in the control group. The etiology of the localized pain patterns in the study ranged from surgical or other traumatic peripheral nerve injuries to stroke.

TARGETING HSP WITH STIMROUTER™

Axillary nerve stimulation via percutaneous leads has been examined in multiple published studies and is the recommended therapy to address HSP. The axillary nerve has a specific effect at the shoulder that is aligned with the symptoms and presentation of PSSP. Contrary to some beliefs, the Axillary nerve does have afferents from the GH joint as well as the cutaneous (regimental patch) and motor components. The motor component provides the best mechanical solution for subluxed shoulder as it provides mechanically efficient reduction, rotation, compression, and elevation of the GH joint via activation of the Teres Minor and Deltoid muscles. All these specific direct effects are compounded with the indirect effects following direct motor excitation and subsequent activation or type Ia, Ib, and II sensory fibers yielding a potential mechanism of action on the majority of the proposed drivers. (Table X; Figure Y) These additional indirect inputs to the CNS has been theorized to play a role in desensitization as they represent “normal” input.

Potential Activation/Mechanism for PNS for PSSP	
Activation	**Mechanism for PSSP**
Direct Response	
α motor neurons (deltoids, teres minor)	Biomechanical Alignment
Type Ia, Ib, II sensory fibers (neuromodulated)*	Gate Theory
Aβ fibers*	Gate Theory and Desensitization
Indirect Response	
Type Ia, Ib, II sensory (physiological)*	Desensitization through “normalized” input
y motor neurons (efferent to muscle spindle)	

* Muscle Spindles, Golgi tendon, Joint and Skin receptors

Table X

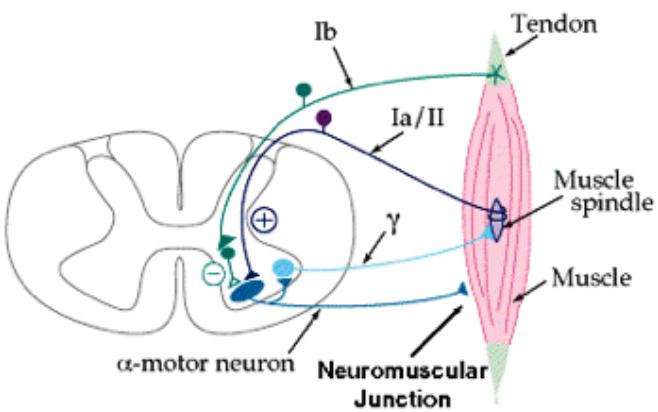


Figure Y

The StimRouter lead, with guidance by a stimulation probe with or without Ultrasound or Fluoroscopy, can be implanted via a posterior lateral approach in less than a 15 minute procedure targeting the axillary nerve just distal to its exit of the quadrangular space. The flexible lead receiver is then located under the skin surface of the posterior/middle deltoid muscle. This placement creates a unique and synergistic energy application to the axillary nerve directly through the lead with the EPT placement over the deltoid and the GH joint. The system has a margin of error built in with respect to EPT placement to accommodate for the dexterity limitations of this patient population. The chosen mechanism of action, depending on the proximity of the lead tip to the axillary nerve and the strength of the field generated by the EPT, can be programmed and/or tuned to result in a desired pain relief level and any additional motor or sensory response, e.g. regimental patch under EPT from muscles or area near both electrical fields. The clinician can work with the patient to find the most appropriate stimulation program and stimulation intensity to achieve paresthesia. Both parameters are ultimately controlled by the patient.

StimRouter's unique characteristics are perfectly suited for tuning to a desired patient response. Providing some level of potentially "corrective" motor stimulation toward better motor function and valuable additional CNS input, while improving pain management, is desirable. The timing of the therapeutic intervention and other factors will play a role in deciding stimulation programs, frequency, and intensity.

CONCLUSION

Post-Stroke or Hemiplegic Shoulder Pain represents a significant unmet medical need primarily as a barrier to patient progression in their prescribed physical rehabilitation toward maximizing their health outcomes. Clinicians are responsible for determining the most appropriate pain management choice(s) that will balance the risks and potential quality of life consequences of that therapy. Recent advances in implantable PNS technology deliver a safe, effective, permanent, non-drug pain management option that has been shown to have expanded benefit. Until there is a more direct, effective treatment for brain injuries like Stroke and Traumatic Brain Injury, consistent investment in technology and clinical work to improve rehabilitation will be play an important role in patient recovery.

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