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Acute and Chronic Pain Suppression through Targeted Peripheral Nerve Application of Focused Ultrasound

Stanford researchers have developed method for targeted application focused ultrasound to peripheral nerves to suppress acute pain.

The prevalence of acute pain is high across multiple other healthcare settings, including inpatient wards, emergency departments, and postoperative units. Acute pain from any injury is frequently inadequately managed; yet, poorly controlled acute pain is associated with significant morbidity. Moderate-severe acute pain is associated with increased risk of developing myocardial ischemia, impaired pulmonary function, ileus, thromboembolism, impaired immune function, infection, and anxiety.

In the US, 100 million patients undergo inpatient and outpatient surgery each year. The vast majority of patients experience pain after surgery, and up to 75% of patients will have moderate-severe pain on the day of surgery. Of the 100 million emergency department (ED) visits in the U.S. each year, acute pain is also one of the most common complaints. Two out of three of ED patients with pain report it as moderate-severe, and yet, only half experience adequate pain relief. Among inpatient adults, up to 80% experience pain and 40% experience severe pain during their hospitalization. Extremity injuries (trauma and surgical) are common reasons for presentation to emergency department and for surgical intervention, and are associated with a high incidence of moderate-to-severe pain, prolonged opioid use, and chronic pain. Acute pain after surgery and trauma typically improves markedly within 2 weeks, but mild-moderate pain often persists for many weeks.

Current acute pain treatment approaches generally fall into two broad categories: of systemic pain medications (often opioids) and neuromodulating techniques, such as peripheral nerve blockade (PNB) with local anesthetics. Opioids remain among the

most commonly used medications for acute pain management; in fact, 40-50% of all inpatients receive opioids during hospitalization. However, opioids are associated with a myriad of adverse outcomes, both short- and long-term. Short-term adverse effects of opioids include respiratory depression, pruritus, nausea, vomiting, and ileus, which worsen patient outcomes and increase patient care costs. Long-term negative effects of acute opioid administration include prolonged opioid use, high-risk opioid use, and the CP development. Further, chronic opioid use after traumatic injury, surgery, and hospitalization is frequent. Long-term opioid use is also associated with an increased risk of developing a large number of negative outcomes, including immunologic and hormonal dysfunction, neurocognitive deficits, hyperalgesia, suicide, and death. Additionally, opioids preferentially inhibit C-fibers over A-delta fibers and thus are better at controlling dull, burning, or rest pain, but not sharp or movement pain. Yet, despite not adequately managing pain, opioids are still widely utilized for acute pain therapy. In fact, more than 70% of surgical patients fill an opioid prescription after surgery, and more than 50% of trauma patients receive an opioid prescription upon discharge. While peripheral nerve blockade (PNB) decreases acute pain in many settings, peripheral nerve blocks have important limitations which have led to their under-utilization in trauma and surgical settings. While only inhibition of pain fibers (A-delta and C fibers) is needed, local anesthetics also block motor (A-alpha) fibers and non-pain sensory (A-beta) fibers, which may increase the risk of patient injury from falls and prevent early participation in physical therapy. Further, while the use of diagnostic ultrasound to find peripheral nerves is straightforward, PNBs can be technically difficult due to the challenges of perineural needle placement. Thus, anesthesiologists' PNB training is complex with expanding requirements for subspecialty training. Additionally, the time required for PNBs is often negatively perceived by surgeons and healthcare providers due to the risk of delays. Single-shot PNBs (single injection of local anesthetic) are short-lived (24 hours) and may result in rebound pain after cessation. Continuous PNBs (a percutaneous indwelling catheter is inserted with the tip next to a nerve for continuous or intermittent local anesthetic infusion) typically last 3-5 days, but require significant clinical follow-up for the provider/patient, and an increasing risk of catheter infection with a greater duration. Additionally, local anesthetic systemic toxicity, with a mortality rate of 10%, is a risk when local anesthetics are injected during PNB.

Pain after trauma and surgeries commonly is moderate-to-severe for 1-2 weeks after the injury and surgery. The vast majority of patients have poorly controlled acute

pain during this period, which worsens patient outcomes.

Ultrasonography was developed in the 1940s to image tissue transcutaneously; diagnostic ultrasound energy delivery to imaged tissues is low. Ultrasound waves pass through human soft tissues with known attenuation factors for each tissue, enabling transcutaneous, (noninvasive) application to both superficial and deep tissues. Similarly to light waves, ultrasound waves can be focused to areas of varying size (relatively easily from 1mm to several mm in diameter) by using a concave transducer, delivering energy noninvasively to a target tissue, and having minimal impact on surrounding tissues. This focused ultrasound (FUS) can be used to deliver 4-6 orders of magnitude greater energy to tissues than is delivered by imaging ultrasound; depending on the FUS parameters used, the energy is transferred to tissue as thermal and mechanical energy. With magnetic resonance imaging (MRI)-guidance, high intensity FUS is used clinically as a noninvasive technique to safely ablate tissue, e.g., prostate cancer and uterine fibroids. Lower intensity FUS can be used for clinical purposes, non-permanently altering tissues.

Currently, FUS is widely investigated for its potential in modulating the central nervous system, specifically to treat diseases such as essential tremor, Parkinson's disease, obsessive-compulsive disorder, neuropathic pain, and depression. Advantages of FUS for transcranial neuromodulation include the ability to noninvasively target deep brain regions, its ability to be directed at very specific and small areas of the brain, and its lack of ionizing radiation. There is increasing evidence that FUS may be an optimal tool for treating peripheral pain conditions. Prior investigations have also studied the effect of FUS on the peripheral nervous system (PNS), finding dose-dependent reversible or permanent reduction in peripheral nerve action potential (AP) amplitudes across different ex vivo and in vivo animal models. Investigators have postulated that FUS may be used to manage some pain conditions, and animal studies suggest further potential for this purpose. However, published investigations into FUS's utility for acute pain management are lacking from the scientific literature.

Injected liposomal bupivacaine, for PNB and local infiltration at the surgical site, was developed to provide extended duration pain management. However, a recent meta-analysis concluded that liposomal bupivacaine does not significantly extend pain relief compared to non-liposomal bupivacaine. ATX-101, a phase II investigational sustained release local anesthetic-polymer, has also been proposed as an adjustable duration for local infiltration and peripheral nerve blockade.

However, injection of local anesthetics is invasive and requires a high level of training to safely guide a needle to a peripheral nerve. Additionally, local anesthetics are direct neurotoxins, and exposure of peripheral nerves to local anesthetics beyond 48-72 hours results in increasing nerve injury (although without known clinically-relevant adverse effects).

The Anderson lab has investigated FUS's potential for acute pain suppression and found that using a distinct set of parameters, FUS 1) preferentially inhibits pain fibers over motor fibers and 2) blocks acute pain for 1-2 weeks after injury.

FUS appears to be a promising modality for reversibly inhibiting peripheral nociceptive fibers without the need for systemic, addicting pharmacologic agents (i.e., opioids). FUS has the benefits of regional anesthesia and 1) is noninvasive, obviating the risk of infection; 2) eliminates the need for local anesthetics which inhibit motor fibers and have potential for systemic toxicity; 3) differentially inhibits nociceptive fibers over motor fibers, thus is unlikely to reduce PT participation or increase the risk of falls; 4) would require significantly less training and post-procedural care to utilize than regional anesthesia; 5) potentially could be employed as early in the chain of care as the battlefield triage station; and 6) may decrease the risk of developing chronic pain after trauma, and thus, reducing CP-associated morbidities (i.e. substance use disorder).

Stage of Development

Proof of concept

Applications

- Acute pain treatment using a distinct set of FUS parameters intermittently or in a pulsatile form

Advantages

- No other focused ultrasound device or procedure currently exists for peripheral nervous system neuromodulation to suppress acute pain.
- The current focused ultrasound method is a desirable alternative to opioid drug treatment for pain treatment.
- The device and procedure are noninvasive

- The current device and method are a non-drug-based method for pain suppression.

Patents

- Published Application: [WO2022266261](#)
- Published Application: [20240115887](#)

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