Temperature-Mediated Nerve Blocks in the Treatment of Pain

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Abstract
Purpose of Review Analgesic hot and cold temperatures have been used for both conservative and ablative therapies for millennia. There are well-known locoregional neurovascular changes associated with the application of heat or ice in the literature and in practice. The oscillation between heat and cold has recently been identified as a synergistic mechanism of action with early translational results in humans.

Recent Findings Recent mechanistic work in the feline model has demonstrated that a reliable, reversible nerve block can be achieved within a temperature range that is non-destructive (15–45°C). The underlying mechanism is a newly described hysteresis in the responsiveness of peripheral nerves to alternating thermal stimuli resulting in nerve blockade. Recently presented feasibility data reports positive results in subjects with occipital pain and peripheral scar pain in terms of pain and associated symptom improvement.

Summary Temperature-mediated changes in pain and sensation have been observed for hot and cold applications at a variety of temperatures. Recent insights into the synergy between preheating followed by cooling resulting in peripheral nerve fiber block has potential in a variety of conditions in which peripheral nerve etiology is noted. Recent findings in chronic headache patients report decreased pain and symptom improvement. Further studies are ongoing to understand the indications for this novel therapy.

Keywords Thermal neuromodulation for pain · Temperature-weight illusion · Drug-free reversible nerve block · Thermal nerve block · Occipital pain treatment

Introduction
The use of thermal treatments in the treatment of pain, swelling, and after trauma is established as a cornerstone of conservative care. The range of therapeutic thermal treatments available in modern medicine represents a continuum of care from temporary therapeutic temperatures (heat or ice) to ablative temperatures (cryoablation or thermal ablation). Quantitative sensory testing (QST) baseline work has established the mean cold-pain threshold of the skin to be ~14°C whereas the heat-pain threshold of the skin is at ~44°C [1].

The accessibility and low cost of ice in the treatment of soft tissue injury make it a core component of the classic RICE (rest, ice, compression, elevation) treatment [2]. Local ice treatment reduces metabolic demand, induces vasoconstriction, and reduces pain through action on local nerve conduction latency and excitability [2, 3]. Ice application is a generally recommended treatment for soft tissue injury due to safety and access, despite a lack of high-quality supporting evidence. Treatment with ice-cold temperatures for the typical 20 min on is generally known to cause numbness in the cooled zone that reverses with warming.

Cold Block Impairs Sensation and Proprioception, but Not Absolute Strength

One group of researchers performed a force replication experiment, in which healthy controls performed an isometric contraction of the ankle dorsiflexors at baseline to establish their maximum voluntary isometric contraction (MVIC) and then performed precision exercises with biofeedback to attempt to...
repeat forces of 20% and 50% of MVIC. [4]. This experiment was repeated after ice immersion (first for 20 min, then for 10 min), with no difference in MVIC but with a significant decrease in precision on repeated strength testing under ice conditions. The authors conclude that cutaneous sensory afferents and their contribution to proprioception are blocked, without any disruption to the deep muscle groups [4]. This makes sense from an evolutionary perspective, as it would be logical to preserve motor function while reducing sensory afferents in the setting of extreme temperatures at either end of the spectrum.

Is It an Illusion or a Nerve Block?

The concept of thermal-mediated nerve blocks is not well-described in the literature. However, it is clear that thermal input is a critical sense when interacting with the physical world. The integration of mechanical and thermal information does not just occur centrally, but also at the level of the cutaneous mechanoreceptor [1, 5]. Prolonged cold exposure of the skin leads to numbness and has the effect of potentiating tactile mechanosensitivity and reducing proprioception [1, 4]. The result is that cold objects are perceived to be heavier than the same object at neutral temperature. This effect, known as Weber’s Phenomenon, is also known as the Temperature-Weight Illusion (TWI) [1, 3]. TWI is an example of partial cold block of mechanoreceptors innervated by Aβ fibers. This is an example of cold neuromodulation: cooling an object increases its apparent heaviness. This is manifest not just in the perception of heaviness, but also in the motor response, which is proportionally exaggerated to the overestimated mass of the object. In other words, because your brain thinks the object is heavier than it is due to blocked sensory input by cold, you reflexively apply more force than necessary to lift the object based on its perceived, but not actual, mass.

Heat Provides Relief, but Burns Before Blocking a Nerve

Ablative therapies are effective with temperatures >45°C and result in a complete irreversible nerve block due to tissue thermocoagulation [6]. Non-burning thermal treatments have long-been established as part of wellness rituals, with the sauna culture serving as the modern iteration of a host of practices, including sweat lodges and hot packs. In this setting, hot therapy is used for its vasodilatory effects, including increasing blood flow and metabolism [7, 8].

In a study of chronic nonspecific neck pain in elderly people, Shin et al. compared thermotherapy combined with neck stabilization exercises to exercises alone on pain, function, and mechanical hypersensitivity [9]. Outcomes reported include the Neck Disability Index (NDI), VAS at rest, VAS with movement, muscle tonometry, and pain pressure threshold determination (PPT) over the levator scapulae, trapezius, and splenius capitis muscles [9]. These measurements were performed before and after each intervention and at the completion of a 10-session program. There was improvement in both groups compared to baseline but the thermotherapy treatment proved superior across multiple domains, including sensitivity and spasm. The PPT improved from 76 to 99% in all three muscle groups with thermotherapy as compared to <25% improvement for exercises alone [9]. The VAS during movement of the intervention group significantly decreased by 66% from 67.5 to 22.8 mm compared to a 25% improvement in the control group from 60.6 to 45.3 mm [9].

Another study evaluated the impact of far-infrared low-temperature sauna (FILTS) set at 60°C on the frailty of elderly patients (n=67) when administered twice weekly for 3 months (24 sessions) [10]. Assessment of frailty included both PROs and physical characteristics, including body mass, cardiovascular fitness (peak VO2), presence of edema, presence and intensity of chronic pain, and disease [10]. At 3-month follow-up, 26.9% of subjects treated with FILTS were noted to have improvements in their frailty score, 70.1% were unchanged, and 3% worsened [10].

Hot or Cold Alone Is Not Optimized for Analgesia

Thermal therapy is a conservative, first-line therapy in clinical, rehabilitation, and sports medicine [11]. Cold therapies provide analgesia and can also reduce inflammation and edema while heat is commonly employed to relieve muscular pain and spams and is known to improve local circulation [11]. At moderate temperatures like those used for rehabilitation and sports medicine, pain relief is temporary and reversible. Applying moderate temperatures for relief of pain is a self-manageable therapy (heating pad, ice pack, etc.). Cryoneurolysis is one form of interventional cold therapy that causes Wallerian degeneration of the axon and the myelin and has the potential to alleviate pain and motor dysfunction in certain conditions [12, 13]. Ablations (thermal, chemical, or surgical) may also be performed for pain relief, though it is known that excessive heating of nerves can cause edema, blood vessel occlusion, severe endothelial cell damage, and demyelination [14•]. This also includes deafferentation pain, weakness and atrophy, dysesthesias, or failure to relieve pain despite destruction of appropriate structures.
Reversible Temperature-Mediated Nerve Blocks Rely on Hysteresis

The innovation that has led to the advent of temperature-mediated nerve blocks is the convergence of two first-line therapies (hot and cold) and combining them in an optimization step to create a dense, reversible, peripheral nerve block. The evidence of a reversible nerve block at moderate temperatures has been elucidated by Zhang et al. [14•]. They observed a hysteresis in which a period of gentle warming prior to cooling created a reversible block of the feline pudendal nerve without burning or freezing [14•]. These results indicate that heating motor A nerve fibers prior to cooling allowed a nerve block to be achieved at a temperature that was non-ablative (Fig. 1A, B). Morgan et al revealed in their more recent study that axonal conduction in C-fibers of the feline tibial nerve can be partially or completely suppressed by locally cooling the nerve to 15–25°C after a preheating (5–35 min) at 45°C [16•]. This insight supports the hypothesis that a reversible thermal nerve could be applied clinically to treat acute and chronic [16•].

The transient receptor potential-vanilloid (TRPV)1 and TRPV2 receptors are known to be present in unmyelinated C fibers and some small Aδ fibers [16•]. These receptors have been shown to be temperature sensitive which makes them an optimal target for this newly elucidated mechanism. TRPV1 receptors are activated at approximately 42°C which may provide insight as to the results of Morgan et al. [16•]. They utilized the temperature 45°C to locally heat the tibial nerve, which would have activated the TRPV1 receptors prior to the cooling period (Fig. 1C, D). The activation of the TRPV1 receptors during the pre-heating period is hypothesized to have caused a series of molecular reactions that sensitized the C fiber to cold temperatures, and neuronal conduction could be blocked at 15–25°C rather than 5–15°C [5]. This mechanism has yet to be clarified. The C-fibers in this experiment exhibited an 80% recovery up to 100 min after block [16•]. This partial recovery could either be due to irreversible damage or activation of cellular mechanisms as mentioned above. Regardless, additional investigations into recovery are warranted. The result of this study demonstrates the possibility of developing a thermal block that would be safe for nerves and also applicable and effective for many painful disorders.

Occipital Nerves Are Ideal Anatomic and Neurobiologic Targets

The posterior neck and occipital regions represent an ideal setting for thermal block in the distributions of the cutaneous occipital nerves, greater occipital nerve (GON), and third occipital nerve (TON). In humans, these nerves emerge from the C2 and C3 posterior rami, respectively, and take a tortuous path around/through the obliquus capitis inferior (OCI), semispinalis capitis (SSC), and trapezius muscles [17]. At the point where the occipital nerves emerge lateral to the external occipital protuberance, they are found reliably within <15 mm of the skin surface at this level on stereotactic topography [17].

Furthermore, the occipital region is an interesting area in terms of neurological crossover, in that the C2-4 central neurons not only include non-trigeminal nociceptive innervation from the posterior dura (intracranial), but also from cutaneous receptor fields (extracranial) [18•]. These cutaneous receptor fields lie in the occipital region yet map to the trigeminal nucleus caudalis, making anesthetic block of the occipital nerves a common practice for the treatment of a variety of headache etiologies manifesting as occipital pain [18•]. These C2-4 central neurons serve as a convergence point for intracranial and extracranial inputs to the trigeminal cervical complex critical to nociceptive transmission and higher-level pain processing.

Which Got Sensitized First, the Head or the Neck?

Noseda et al. sought to answer the chicken-and-egg question surrounding the common feature of occipital headaches across a variety of primary and secondary headache conditions [18•]. They performed anterograde tracing of the rat C2 DRG neurons innervating the posterior dura using immunofluorescence, followed 3 weeks later by retrograde labeling from the posterior dura to the C2-4 DRGs [18•]. They visualized occipital nerve axon branches entering the skull via the occipital-periotic suture lines as well as through emissary canals in the occipital bone [18•]. These emissary nerves further support the presence of occipital pain as a common feature among a variety of conditions with disparate etiologies since at least some of the nociceptive axons innervating the dura of the posterior fossa actually originate outside the skull [18•].

Nerve Blocks Are Not Predictive of Neuromodulation Outcomes

Modulation of these nerves and receptive fields has been reported using a variety of neurostimulator arrays, from purpose-built devices to repurposed spinal cord or peripheral nerve stimulators for a variety of conditions, including chronic migraine, cluster headache, and occipital neuralgia [19–25]. Interestingly, response to occipital nerve block has been shown to not be predictive of a response to occipital stimulation, with 39% concordance reported in the ONSTIM study and a recent review by Kinfe et al. [23, 26]. Occipital nerve
blocks are commonly performed for both acute and chronic headache conditions in the authors’ clinic with success, and has been reported in the literature extensively [18, 27–30] A recent systematic review and meta-analysis of six RCTs in the Emergency Medicine literature reviewed GON block for the treatment of migraine [30]. The analysis revealed significant
benefits from the occipital nerve block in terms of pain, number of headache days, and medication use, but no significant reduction in monthly headache days [30]. Occipital nerve blocks can be reliably performed with landmark, ultrasound, or fluoroscopic approaches by a variety of clinicians [29, 31–35].

Recent Findings in Headache

Temperature-mediated nerve blocks are in the process of being explored in the human model. Most commonly, it has proven to be successful in treating neuralgia of palpable superficial nerves, like those implicated in a variety of headache conditions. The investigational protocol to determine feasibility of thermal nerve block was developed and applied in the clinical space in an attempt to address these headache disorders.

Our group has previously presented data on an observational study of a single thermal nerve block intervention on 42 patients living with chronic headaches or migraine. (Fig. 1E, F) The average baseline pain score for these subjects was 6.1 ± 1.7, which decreased to 2.6 ± 2.5 after treatment (58% average pain reduction; p < 0.05) [15]. Nearly half (48%) of subjects ended with all head/neck pain at NRS of 1 or below, and most subjects (62%) had an ending NRS pain score of 3 or below [15]. Interestingly, 17% of subjects ended reporting 0/10 head and neck pain [15]. The time frame for return of head and neck pain in these subjects was variable from weeks to months. The primary safety concern with this therapy was skin burn at the area where the therapy was applied. The 42 subjects were closely observed during the thermal portion with a strict adherence to a time and temperature-limit protocol so as to minimize the risk of skin burn. Blistering of the skin was noted in one subject that did resolve with local wound care. Further investigation into the effectiveness and safety of this therapy and advancements in product development is warranted.

Discussion

Thermal treatments have been employed for millennia, and ablative therapies with cryoanalgesia and thermocoagulation are commonly performed for a variety of conditions. Peripheral nerve blocks are a cornerstone of modern regional anesthesia and post-surgical and post-traumatic analgesia, but require skilled clinicians and equipment. The concept of temperature-mediated nerve blocks is compelling in their elegant simplicity, safety, and ease of use for self-management. Hot and cold treatment has been established as a component of conservative care and is accepted by most as a safe first-line treatment. Multiple studies are ongoing investigating the clinical application of thermal-mediated nerve blocks for a variety of superficial indications. Furthermore, fully implantable systems may be developed in the future to achieve reversible nerve block using this paradigm.

Figure 1: Figure 1A shows that heating prior to cooling lowered the temperature at which a complete cold block was formed in motor A nerve fibers of the feline pudendal nerve. Figure 1B

Declarations

Conflict of Interest AMS and AMK are employees of the Center for Interventional Pain and Spine (CIPS). MAF and PSK have stock options in Thermaquil, LLC. CIPS received contracted research payments from Thermaquil.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published or presented and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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