

## iovera<sup>o</sup> system Peer-Reviewed Publications

Clinical Study Title	Author	Journal	Summary
Cryoneurolysis to treat the pain and symptoms of knee osteoarthritis: a multicenter, randomized, double-blind, sham-controlled trial	Radnovich	Osteoarthritis and Cartilage 2017	<ul style="list-style-type: none"> <li>• Randomized, double-blind, sham-controlled, multicenter trial with a 6-month follow-up in 180 patients at 17 sites with mild-to-moderate knee OA.</li> <li>• Compared to the sham group, patients who received iovera<sup>o</sup> treatment had a statistically significant greater change from baseline in the WOMAC pain subscale score at Day 30 (p=0.0004), Day 60 (p=0.0176), and Day 90 (p=0.0061). Patients deemed WOMAC pain responders at Day 120 continued to experience a statistically significant treatment effect at Day 150.</li> <li>• Most expected side effects were mild in severity and resolved within 30 days. The incidence of device- or procedure-related adverse events was similar in the two treatment groups with no occurrence of serious or unanticipated adverse device effects (ADE).</li> <li>• Cryoneurolysis of the IPBSN resulted in statistically significant decreased knee pain and improved symptoms compared to sham treatment for up to 150 days, and appeared safe and well tolerated.</li> </ul>
Ultrasound-guided percutaneous cryoneurolysis for treatment of acute pain: could cryoanalgesia replace continuous peripheral nerve blocks?	Ifeld	British Journal of Anaesthesia 2017	<ul style="list-style-type: none"> <li>• Review article which cites examples of iovera<sup>o</sup> treatment outcomes and explores the risks and benefits of its use.</li> <li>• Concludes that "current evidence suggests that ultrasound-guided percutaneous cryoanalgesia holds enormous potential for making a dramatic leap forward in providing long term analgesia far surpassing typical continuous peripheral nerve blocks, with minimal risk and a lower patient burden."</li> </ul>
Ultrasound-guided percutaneous cryoneurolysis providing postoperative analgesia lasting many weeks following a single administration: a replacement for continuous peripheral nerve blocks? -A Case Report-	Ifeld	Korean Journal of Anesthesia 2017	<ul style="list-style-type: none"> <li>• A case report of two total shoulder arthroplasty patients treated with preoperative suprascapular nerve cryoneurolysis instead of perineural local anaesthetic infusion demonstrated that potent analgesia was provided for 2–4 weeks, obviating catheter care, infusion pump dependence, local anaesthetic toxicity risks and reservoir burden, as well as decreasing the risk of infection.</li> <li>• A case report of three patients treated with ultrasound-guided infrapatellar cryoneurolysis experienced up to 4 months of cutaneous sensory deficits.</li> </ul>
Ultrasound-Guided Percutaneous Cryoneurolysis fo Acute Pain Management: A Case Report	Gabriel	Anesthesia & Analgesia Case Reports May 2017	<ul style="list-style-type: none"> <li>• Three different cases in which ultrasound-guided percutaneous cryoneurolysis was performed to treat acute pain: 1 patient with refractory incisional pain after percutaneous nephrolithotomy; 1 patient with burns to the foot; and 1 patient with pain from iliac crest grafting. All patients reported reductions in pain for at least two weeks.</li> <li>• Concludes that cryoneurolysis is "a novel method for acute pain management" as "Acute pain associated with surgery or injury is a challenge to treat with local anesthetic-based regional anesthesia techniques when the anticipated pain duration exceeds a few days."</li> </ul>

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Percutaneous freezing of sensory nerves prior to total knee arthroplasty	Dasa	The Knee 2016	<ul style="list-style-type: none"> <li>Retrospective chart review of 100 patients: 50 patients with standard-of-care knee replacement (control group) compared to 50 patients with iovera<sup>o</sup> performed 5 days prior to the standard-of-care knee replacement.</li> <li>A significantly lower proportion of patients in the iovera<sup>o</sup> group had a length of hospital stay of <math>\geq 2</math> days compared with the control group (6% vs. 67%, <math>p &lt; 0.0001</math>) and required 45% less opioids during the first 12 weeks after surgery.</li> <li>The iovera<sup>o</sup> group reported a statistically significant reduction in symptoms at the six- and 12-week follow-up compared with control group and within-group significant reductions in pain intensity and pain interference at two- and six-week follow-up, respectively.</li> </ul>
Novel cryoneurolysis device for the treatment of sensory and motor peripheral nerves	Ifeld	Expert Review of Medical Devices 2016	<ul style="list-style-type: none"> <li>Extensive review article which details the history and mechanisms of action of cryoneurolysis as well as the safety and efficacy of the modality in several clinical applications.</li> <li>Concludes that "changes in the US healthcare system such as a push for the reduction of opioid use and the incorporation of Diagnostic Related Group codes, as well as recent technological advances including a handheld unit that allows for treatment of superficial nerves while protecting the skin from damage, may contribute to the resurgence of cryoneurolysis for the treatment of peripheral nerves."</li> </ul>
Development and validation of a new method for locating patella sensory nerves for the treatment of inferior and superior knee pain	Hu	Journal of Experimental Orthopaedics 2015	<ul style="list-style-type: none"> <li>Anatomical study designed to define and validate a new treatment approach to treat the sensory nerves of the patella.</li> <li>Data from transcutaneous electrical nerve stimulation and ultrasound on 25 healthy volunteers were used to map the nerves and create a treatment line. Nerve branching patterns through these lines were then validated in 15 fresh cadaver specimens.</li> <li>Results demonstrated that the iovera<sup>o</sup> treatment lines captured the vast majority of nerve branching variations.</li> </ul>
Wallerian Degeneration and Recovery of Motor Nerves After Multiple Focused Cold Therapies	Hsu	Muscle & Nerve 2015	<ul style="list-style-type: none"> <li>Prospective study evaluated the effects of single and 3 repeat iovera<sup>o</sup> treatments on a sciatic nerve rat model.</li> <li>There was consistent weakening of physiological function and restoration of normal function after each treatment. Histological findings showed axonal degeneration with no disruption to the epineurial or perineurial structures.</li> <li>Low-temperature treatment of motor nerves did not result in permanent or long-term changes to nerve function or structure.</li> </ul>
Reduction in muscular motility by selective focused cold therapy: a preclinical study	Hsu	J Neural Trans 2014	<ul style="list-style-type: none"> <li>Prospective study demonstrated the reduction in motility of muscle groups through application of low temperatures to nerves in 27 subjects in a rat model.</li> <li>The application of cold onto the rat tibial nerve resulted in temporary reduction of physiological function of the hind limb. Histological observations of the nerve revealed demyelination and axonal degeneration by 2 weeks post-treatment followed by complete axonal regeneration and remyelination at 16 weeks.</li> <li>Application of low temperatures to peripheral motor nerves resulted in temporary denervation and loss of function of the treated hind limb. Low temperature treatment on motor nerves did not result in any permanent or long-term changes to function and structure of the nerves.</li> </ul>

The Myoscience iovera<sup>o</sup> system is used to destroy tissue during surgical procedures by applying freezing cold. It can also be used to produce lesions in peripheral nervous tissue by the application of cold to the selected site for the blocking of pain. It is also indicated for the relief of pain and symptoms associated with osteoarthritis of the knee for up to 90 days. The iovera<sup>o</sup> system is not indicated for treatment of central nervous system tissue.