Iovera, Pacira Pharmaceuticals Inc.

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Device

Iovera is a handheld system that uses freezing cold temperatures to produce lesions in peripheral nervous tissue to block pain during surgical procedures. The device uses nitrous oxide (N_2O) to create cryoneurolysis (a 'cold zone' reaching -88 degrees C) in targeted locations which produces temporary degeneration of the axon and myelin sheath that blocks nerve signals. According to manufacturers, regeneration of the axon occurs at a rate of 1 to 2 mm/day[2], eventually resulting in fully regenerated, fully restored nerve signaling.[1]

FDA Approval

The iovera system from Pacira, Pharmaceuticals, Inc. was approved in 2021 and carries an FDA indication as a device used to destroy tissue during surgical procedures or create lesions in peripheral nervous tissue using extreme cold. It is additionally indicated for pain relief associated with knee osteoarthritis for up to 90 days. (510(k) Number: K211334).

There are multiple predicate devices associated with the iovera system. All such devices can be found in the 510(k) Premarket Notification Database.

Society Guidelines

In their *Clinical Practice Guideline on Management of Osteoarthritis of the Knee (3rd Edition)*, the American Academy of Orthopedic Surgery states, "Denervation therapy may reduce pain and improve function in patients with symptomatic osteoarthritis of the knee."[2] However, they note the strength of this recommendation is limited given inconsistent evidence and bias. More evidence with specific sub-group and cost-effectiveness analyses is recommended.[2]

Clinical Data

There is accumulating evidence evaluating cryoneurolysis. A sample of the available literature is provided below.

- A systematic review by Junker et al. (2021) analyzed literature published before 2020 to assess methods of non-pharmacologic analgesia on post-operative opioid use. Secondary outcomes included non-opioid medication use, pain scores, and other patient outcomes. A total of 6 studies were included in the review, which included the non-pharmacologic methods of percutaneous nerve stimulation (n=3), percutaneous cryoneurolysis (n=2), and auricular acupressure (n=1). The authors concluded that all 3 methods have the potential to reduce opioid consumption in the post-operative period, with cryoneurolysis having an advantage in postoperative pain control and operational outcomes.[3]
- A randomized controlled trial by Mikhalo et al. (2021) assessed the effectiveness of cryoneurolysis (n=62) versus standard of care (n=62) before total knee arthroplasty (TKA) in reducing total postoperative opioid use at a single center. Cryoneurolysis was administered via the iovera device and post-operative outcomes assessed at 72 hours, and then 2, 6, and 12 weeks after surgery. After statistical analysis, the authors concluded that cryoneurolysis did not significantly reduce opioid consumption from surgery to 6 weeks post-op when analyzed as intent-to-treat. However, there was a noted reduction in per-protocol analyses. Limitations of the study included a lack of sham control group and the use of a single site. Funding for this study was provided by Pacira BioSciences, Inc.[4]

- A randomized controlled trial by Radnovich et al. (2017) assessed the use of cryoneurolysis (via iovera) in the treatment of pain in patients with osteoarthritis of the knee. Patients were randomized into active treatment (n=121) and sham groups (n=59) and primary endpoints were assessed using the Western Ontario and McMaster Osteoarthritis Index pain score. Authors noted a statistically significant decrease in knee pain and overall improved outcomes in the cryoneurolysis treatment group. Limitations of this study include potential patient awareness of group assignment. Funding for this study was provided by Pacira BioSciences, Inc.[5]
- A retrospective analysis by Lung et al. (2022) assessed total opioid morphine milligram equivalent consumption for patients receiving pre-operative cryoneurolysis (via iovera) prior to primary TKA. Other outcomes collected included range of motion scores, ambulation distances, and patient reported outcomes surveys as examples. The authors reported that the use of morphine milligram equivalents was decreased overall for patients receiving cryoneurolysis, although these results were not statistically significant. Other measured outcomes showed similar results. The authors concluded cryoneurolysis is an effective therapy to integrate into a patient's pain management plan. Limitations of this study included retrospective design and lack of randomization.[6]
- A pilot case series by Roth et al. (2022) used billing codes to identify patients (n=10) who received TKA, cryoneurolysis, and physical therapy at a single site. Cryoneurolysis was administered via the iovera device and outcomes data collected included post-operative pain scores, pain scores during physical therapy, and range of motion during physical therapy sessions. The authors noted that patients reported a reduction in pre-operative pain after receiving cryoneurolysis, which may suggest the effectiveness of this treatment if the source of pain is identifiable. Limitations of the study included a small sample size and the use of a single study site.[7]

Physician Advisor Insight

A panel of orthopedic surgeons within our HealthTrust Physician Advisor Network offered the following insight with regard to using cryotherapy, like the iovera device[8]:

- May be beneficial for:
  - Patients with severe pre- or post-op pain
  - Severe arthritis
  - Painful TKA
  - Patients with arthritis that is unresponsive to injections, NSAIDs, and who are not healthy enough for a TKA
- Other patient criteria may include:
  - Too young for TKA
  - Significant arthritis, fibromyalgia, or peripheral neuropathy
  - Current treatment for pain management
  - Patients who cannot tolerate narcotics, or who have a history of narcotic abuse
  - Post-trauma patients with history of reconstruction
- Safety consideration include:
  - Risk for unintended neurologic injury
  - Potential for nerve "damage"
  - Potential for "failure of treatment"

Summary/Considerations

The current evidence surrounding cryoneurolysis is complex and most studies reviewed suggested that more research is needed to better understand its use.[2,4-6]

References

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