RecoveryRx®

Mechanism of Action

The science behind postoperative pain

Pain, a complex sensory experience, is a physiological process for the brain to communicate damage or a risk of damage to the tissues in the body. It is normally composed of the following major components: 1) Nociceptive pain; 2) Inflammatory pain; and 3) Neuropathic pain. Surgical procedures involve a range of disruptions to bodily tissues, resulting in both nociceptive and inflammatory pain, which resolve quickly as the tissues heal. However, surgery also leads to nerve damage, which results in neuropathic pain. Nerve tissue heals slowly, so neuropathic pain commonly takes 1-3 months to resolve. Statistics show that for as many as 40% of postoperative patients, neuropathic pain continues beyond this time, and can transition into chronic neuropathic pain, a condition referred to as surgery-induced neuropathic postoperative pain (SNPP). A critical factor that contributes to the emergence of SNPP in individuals is the onset of central sensitization (CS).

Onset of Central Sensitization (CS)

Injury information is transmitted as signals to the brain primarily through two main types of nerve fiber: *A-delta* and *C fibers*. Typically, these signals reduce and finally subside over a period of days. However, when the barrage of neural activity is severe, causing intense pain and/or sustaining for an extended period, the nerve fiber activity is fundamentally altered. Such alterations are referred to as central sensitization (CS). In simple words, CS refers to pain hypersensitivity as a result of amplification of neural signaling within the central nervous system (CNS).

CS results in CNS dysfunction in such a way that nerve fibers that are not intended to communicate pain sensations get recruited into pain pathways. For example, *A-alpha* and *A-beta* fibers that typically communicate sensations like touch and pressure, now communicate pain. This typically appears in two forms – allodynia and hyperalgesia. The former is a condition where stimuli which are normally not painful, like warmth or touch, are coded as pain. On the other hand, hyperalgesia amplifies the pain caused by even mildly painful stimuli like pressure. The individual's pain threshold thus lowers, and eventually becomes chronic pain if left untreated.

Limitations of NSAIDS and Opioids

While nociceptive, inflammatory, and neuropathic pain can all lead to CS, the risk of developing central sensitization leading to chronic pain (SNPP) is much greater for the latter, owing to the slow recovery time of damaged nerve tissues. Pharmacotherapies like NSAIDs and opioids are known to effectively reduce the risk of developing CS by diminishing the nociceptive and inflammatory components of pain. However, they do not directly address neuropathic pain, nor do they address the changes occurring in the CS and the development of SNPP. These limitations, in addition to their life-threatening side effects, highlight the need for a safe therapy that directly addresses the CS function and increases pain threshold.

RecoveryRx® Mechanism of Action

Very limited treatment strategies have been shown to be effective in reversing SNPP once it develops, so the goal should be early intervention to reduce the risk of SNPP from developing. The key to reducing SNPP risk is to raise pain thresholds either pre-surgically or peri-surgically. This can be done by providing a barrage of non-painful stimuli to the central nervous system (CNS) via the A-*alpha* and A-*beta* nerve fibers. This counterintuitive approach can be understood through *habituation* and *sensitization* that occur in the peripheral nervous system.

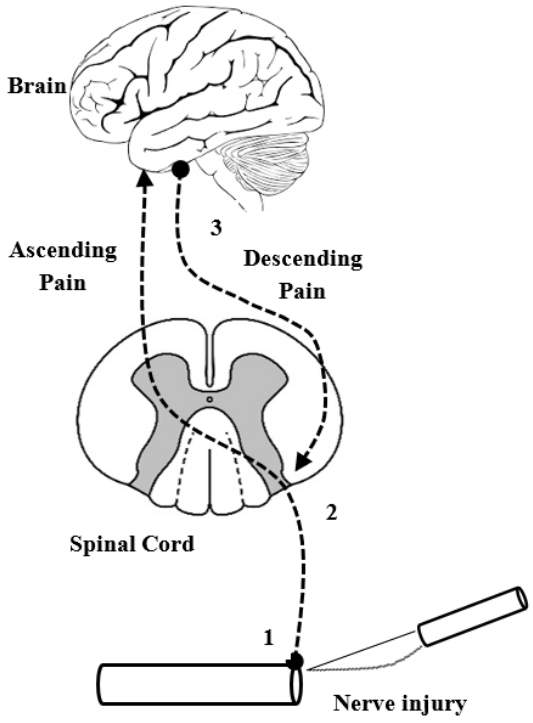

Figure 1:

1) Nerves severed during surgery produce chemicals and abnormal signals that increase pain signaling

2) Abnormal nerve activity alters excitability and responsiveness at the dorsal horn (central nervous system), amplifying pain and inducing central sensitization

3) Decreased modulation of inhibitory pain pathway further amplifies pain perception. Central sensitization can occur within hours of tissue injury.

Adapted from Kehlet H. et.al. The Lancet Vol. 367 Persistent postsurgical pain: risk factors and prevention, pages 1618-1625 (2006)

The peripheral nervous system continuously receives large amounts of sensory information from the environment. The background level of this activity is referred to as “afferent noise”. In order to send only relevant information to the brain, the peripheral system constantly adapts to the background noise level, so that only stimuli above the background noise level are sent to the CNS for processing. The raising of the background noise threshold is referred to as *habituation* while the lowering of the background noise level threshold is referred to as s*ensitization*.

Slowing, or preventing, the development of CS requires a sustained presence of a non-painful, habituating stimulus to the CNS, essentially “instructing” the system to raise sensation thresholds - this is what the RecoveryRx does.

The RecoveryRx produces low intensity (non-thermal), radiofrequency, electromagnetic energy pulses which increases afferent nerve activity originating in the tissue region where nerve damage will, or has, occurred. These pulses are repeated at the relatively high-rate of 1000 times a second. This rate is critical since the A-alpha and A-beta nerves specifically respond to higher frequencies of stimulation. Using the RecoveryRx over the surgical area, peri-surgically, increases A-alpha and A-beta activity. The CNS then

“sees” the RecoveryRx produced nerve responses as increased afferent noise, resulting in a habituation-like response, leading to a rise in the pain threshold level soon after the surgery and in turn serves to reduce the risk of SNPP developing.

Claims and Clinical Studies

A) RecoveryRx claims and evidence:

Reduces postoperative pain [1] [2] [4] [5]

Reduces inflammation [4] [5]

Reduces edema [1] [4] [5]

Reduces surgical wound exudate [1]

Positive effects on wound healing [1] [4] [5]

Favorable risk-benefit ratio [4]

May be effective to reduce post amputation intractable pain [3]

Feasible for ambulatory use [5]

Provides patient satisfaction [1] [3]

Easy to use [2] [3] [4] [5]

Provides low provider/patient burden [4] [5]

Reduces NSAID use [1] [2]

Reduces opioid medication use [1] [2] [4] [5]

Reduces analgesic side effects [1] [2] [5]

Can be used overnight [1] [3] [4] [5]

Safe to use [1] [2] [4] [5]

24-hour use [1] [2] [3] [4] [5]

No harmful adverse effects [1] [2] [3] [4] [5]

No localized irritation [4] [5]

Can be used with other medications [1] [2] [3] [4] [5]

References

[1] Khooshideh M, Latifi Rostami SS, Sheikh M, Ghorbani Yekta B, Shahriari A. Pulsed Electromagnetic Fields for Postsurgical Pain Management in Women Undergoing Cesarean Section: A Randomized, Double-Blind, Placebo-controlled Trial. *Clin J Pain*. 2017;33(2):142-147. doi:10.1097/AJP.0000000000000376

[2] Rawe IM, Lowenstein A, Barcelo CR, Genecov DG. Control of postoperative pain with a wearable continuously operating pulsed radiofrequency energy device: a preliminary study. *Aesthetic Plast Surg*. 2012;36(2):458-463. doi:10.1007/s00266-011-9828-3

[3] Ilfeld BM, Said ET, Abdullah B, Finneran Iv JJ. Treating Intractable Postamputation Pain with Noninvasive, Wearable, Nonthermal, Pulsed Shortwave (Radiofrequency) Therapy: A 12-Patient Case Series. *Am J Case Rep*. 2022;23:e937549. Published 2022 Aug 17. doi:10.12659/AJCR.937549

[4] Engy T Said, John J Finneran IV, Rodney A Gabriel, Jacklynn F Sztain, Scott T Ball, Krishna R Cidambi, Baharin Abdullah, Brian M Ilfeld. Noninvasive, Wearable, Pulsed Shortwave (Radiofrequency) Therapy for Analgesia following Knee and Hip Arthroplasty: A Case Series. Archives of Clinical and Medical Case Reports 6 (2022): 758-762.

[5] Ilfeld BM, Said ET, Gabriel RA, et al. Wearable, noninvasive, pulsed shortwave (radiofrequency) therapy for analgesia and opioid sparing following outpatient surgery: A proof-of-concept case series [published online ahead of print, 2022 Dec 4]. *Pain Pract*. 2022;10.1111/papr.13188. doi:10.1111/papr.13188

B) Clinical Summary

1. C-Section Study

Introduction:

Giving birth by Cesarean delivery is a relatively common procedure in the United States, representing 32% (1.26 million) of all births in 2016 [1]. Globally, the rates of C-section surgeries have nearly doubled over the past 15 years, from about 12% of all births to 21% of all births [2]. Nikolajsen et al. [3] reported that although post-operative pain from Cesarean delivery is resolved in most women by three months, 12.3% report persistent abdominal scar pain at follow-up visits 10.2 months (range 6.1-17.6 months) after surgery. This pain affected activities of daily living, including the ability to care for their newborn. In this cohort, 5.9% reported pain occurring on a daily or near-daily basis. Patients who had developed chronic postoperative pain had a significantly higher recall of severe acute post-operative pain. As noted previously, high acute postoperative pain is a major risk factor for the development of chronic pain. These findings were confirmed in a more recent study, which indicated that the incidence of persistent pain at 1 year was higher in women with higher acute pain levels after C-section surgery [4]. A 2017 study published in the journal of Obstetrics and Gynecology indicated that the amount of opioids prescribed after Cesarean delivery generally exceeded the amount consumed by a significant margin [5]. Providing effective, multimodal analgesia following C-section surgery may lead to an opioid-sparing effect and limit the availability of residual opioid pills.

Trial Design:

A randomized, placebo-controlled, double-blinded parallel group study was performed to investigate the effectiveness of RecoveryRx in treating postoperative pain in 72 women who underwent cesarean section surgery. These women presented with the following average baseline demographics: 26.1 years of age, gestation period > 37 weeks and singleton uncomplicated pregnancy. Thirty-six patients were assigned to the active device and 36 to the placebo groups in a randomized manner. Subjects were instructed to use the device for 24 hours/day for a total of 7 days. The device was attached over the incision site using medical tape. Patients were advised to use pain medications as needed.

Participants were asked to report their pain intensity on the basis of a Visual Analog Scale (VAS), ranging from 0 (no pain) to 100 (worst imaginable pain), and the pain intensity was evaluated at 2, 4, 6, 12, and 24 hours after surgery. After discharge, participants were asked to record their pain intensity on the second, the fourth, and the seventh postoperative days. Medication use was also logged regularly.

Results:

Only 36% women in the active PEMF group experienced severe postoperative pain within 24 hours postoperatively, while 72% reported experiencing this in the placebo group. VAS scores for postoperative pain were significantly lower in the active-PEMF group in all the measured periods within the early and the late postoperative periods. Use of analgesics during the first 24 hours after the surgery was also 1.9 times lower in the active-PEMF group than the placebo-PEMG

group. Moreover, the total analgesic use during the seventh postoperative day was 2.1-times lower in the active-PEMF group than in the sham group. Seven days postoperatively, patients in the active-PEMF group had better wound healing with no exudate, erythema, or edema.

Conclusion:
PEMF treatment after C-section decreases postsurgical pain, analgesic use, and surgical wound exudate and edema significantly, and is associated with a high level of patient satisfaction.

2. Breast Augmentation Study

Introduction:

Breast augmentation is the number one cosmetic surgical procedure, with more than 300,000 surgeries performed in the United States in 2017 [6]. Chronic pain following breast augmentation surgery is common, with one study reporting that 25% of women experienced chronic pain for a mean follow up period of 27 months [7]. Another study indicated that sensory changes and chronic pain were common even after a mean follow up period of 31.8 months following breast augmentation surgery [8]. In that study, 75.8% reported sensory changes over the breast, 62% reported touch-evoked pain and 38% used pain descriptors that met the diagnostic criteria for neuropathic pain. The severity of postoperative pain following breast augmentation is known to be a major risk factor in the development of chronic pain [9]. It is perhaps not surprising that a high number of opioid analgesics are routinely prescribed following breast augmentation [10]. An effective adjunctive to existing multimodal analgesic regimens following breast augmentation surgery can reduce acute postoperative pain, lower the risk of developing chronic pain and preclude the need for excessive opioid prescriptions.

Trial Design:

A double-blinded, placebo-controlled, randomized study was performed to determine the effectiveness of RecoveryRx in postoperative pain after breast augmentation. Silicone breast implants were used for all the 18 subjects recruited. All subjects presented with the following average baseline demographics: 31.6 years of age, weight of 134 lbs. and height of 5.52 ft. 10 patients were provided with active devices and 8 were provided with placebo devices in a randomized manner.

At completion of the operation, a baseline score was assessed for each subject using a Visual Analog Scale (VAS) ranging from 0 (no pain) to 10 (extreme pain). The pain scores were logged in the a.m. and p.m. along with medication use for each patient.

Results:

The VAS scores for the active group were significantly lower on postoperative day 1. By day 7, the baseline VAS remaining in the active group was 7.9% versus 38% in the placebo group. Moreover, narcotic pain medication use was also lower in the patients from the active group. No side effects were reported by any of the subjects.

Conclusion:

Postoperative pain is significantly lower with Pulsed Radiofrequency energy (PRFE) therapy. According to the findings, PRFE therapy in this form is an excellent, safe, drug-free method of postoperative pain control.

3. Phantom Limb Pain Study

Introduction:

Phantom and residual limb pain are a common occurrence postamputation. Some studies report as many as 50% to 85% of people develop persistent pain postamputation, which significantly impacts their physical and mental health [11]. It is estimated that around 1.6 million people in the United States are currently living with the loss of a limb [12]. Furthermore, it is estimated that this number could grow to more than 3.5 million by 2050, especially since diabetes, a major cause for amputations, is growing rapidly in the US [13].

Study Design:

A case series investigated the effectiveness of RecoveryRx in treating persistent, intractable phantom and/or residual limb pain unresponsive to multiple previous invasive treatments in 12 patients. The nine male and three female subjects presented with the following average baseline demographics: 66 years of age, 175 cm of height, 69 kgs of weight, and BMI of 25. All 12 subjects had intractable phantom limb pain following a transfemoral or transtibial amputation with a pain intensity of at least 3 on a numeric pain scale from 0 (no pain) to 10 (extreme pain) at least daily for more than 1 year. After providing each patient with 1 RecoveryRx device and recording a history and baseline pain levels, patients were contacted once within the first week and then weekly for 5 weeks.

Results:

Of the 12 individuals, 7 (58%) reported their phantom and/or residual limb pain as “very much improved”. While 1 (8%) patient reported “moderate” improvement, 4 (33%) experienced minimal/no change. Of the 8 responders, worst and average phantom limb pain improved a mean (SD) of 4.0 (2.9) and 4.2 (1.8) points on the 0 to 10 numeric rating scale, respectively. Worst and average residual limb pain improved 5.4 (3.7) and 3.5 (2.4) points, respectively.

Conclusion:

The cases suggest that RecoveryRx can be a potentially effective treatment for intractable postamputation pain. While there was no control group, a strong placebo effect for a majority of patients seems improbable, especially since all of them had experienced 2 to 34 years of phantom limb pain and had received multiple forms of treatment without relief.

4. Knee and Hip Arthroplasty Study

Introduction:

Persistent post-surgical pain (PPSP) is a major clinical problem associated with knee and hip arthroplasty. Studies indicate that 7%-23% and 10%-34% of patients report significant pain after total hip arthroplasty and total knee arthroplasty, respectively [14]. Since osteoarthritis of the knee and the hip is one of the most prevalent chronic disorders in the elderly population, a considerable increase in people seeking total joint replacement surgery is expected.

Study Design:

A case series investigated the effectiveness of RecoveryRx in treating postoperative pain and reducing opioid requirement following unilateral total knee and hip arthroplasty in 7 patients. The 4 female and 3 male patients presented with the following average baseline demographics: 64 years of age, weight of 79 kg, height of 171 cm, and BMI of 26.8. Out of the 7 subjects, 2 had undergone unilateral total knee arthroplasty while 5 had undergone unilateral total hip arthroplasty. Each patient was provided with 1-2 RecoveryRx devices and were instructed to wear them continuously through postoperative day 30. Subjects were contacted to report pain level on a numeric rating scale of 0 (no pain) to 10 (extreme pain) on postoperative days 1, 2, 3, 4, 7, 14, 28, and 35.

Results:

The average daily pain at rest and with movement was a median of 0-4 for the entire follow-up period. For the first two days post-operation, the maximum pain was a median of 5 and 6. A constant decline in maximum pain was observed and it fell to 0 by day 35. Out of the seven patients, three did not use opioids at all, and four required 0-7.5 mg of oxycodone daily. Moreover, no side effects, localized irritation, or complications were identified.

Conclusion:

Considering the ease of placement, few contraindication, low provider/patient burden, lack of systemic side effects and serious adverse events, RecoveryRx could be an effective analgesic for knee and hip arthroplasty and could possibly obviate opioid requirements.

5. Umbilical and Inguinal Hernia Study

Introduction:

Postoperative pain is a primary concern after ambulatory surgeries since it is often difficult to concurrently provide adequate analgesia for pain relief while minimizing opioid requirements to avoid side effects.

Study Design:

A proof-of-concept case series investigated the effectiveness of RecoveryRx in treating postoperative pain following outpatient herniorrhaphy and breast surgery in 7 individuals. Out of the seven subjects, three underwent ambulatory umbilical hernia repair, two underwent ambulatory inguinal hernia repair, and the remaining two underwent bilateral breast surgery, all moderately painful. The four female and three male patients presented with the following average baseline demographics: 51 years of age, 165 cm height, weight of 76 kg, and BMI of 27.6. All subjects were provided with 1 or 2 RecoveryRx devices and instructed to use it according to the instructions provided with the device for 30 days. Patients were contacted on postoperative days 1, 2, 3, 4, 7, 14, 28, and 35 to report pain levels on a numeric rating scale of 0 (no pain) to 10 (extreme pain).

Results:

Average resting pain scores measured on the 0–10 numeric rating scale were a median of 0 during the entire treatment period. Further, on postoperative days 1 and 2, average pain with movement was a median of 3 and 1.5, respectively, but subsequently fell to zero for the remaining time points. Similarly, maximum pain daily fell from median 4 on day 1 to 1 on day 4, and 0 thereafter. Six patients avoided opioid use entirely, while the remaining individual required 5 mg of oxycodone on day 1. No side effects or complications were noted.

Conclusion:

The case study indicates that ambulatory use of the RecoveryRx is feasible and may be used as an effective analgesic. Moreover, it could possibly obviate opioid requirements following outpatient herniorrhaphy and breast surgery.

References

[1] CDC, "National Center for Health Statistics," 2016. [Online]. Available: https://www.cdc.gov/nchs/fastats/delivery.htm. [Accessed 9 January 2023].

[2] Lancet, "Optimising caesarean section use," 12 October 2018. [Online]. Available: https://www.thelancet.com/series/caesarean-section. [Accessed 9 January 2023].

[3] Nikolajsen,L et.al.;, "Chronic pain following Cesarean section," Acta Anasthesiol Scand, vol. 48, pp. 111-116, 2004.

[4] Kain, Peter MD et al.;, "Persistent Pain After Cesarean Delivery and Vaginal Delivery: A Prospective Cohort Study," Anasthesia & Analgesia, vol. 123, no. 6, pp. 1535-45, 2016.

[5] Bateman, Brian T MD;, "Patterns of Opioid Prescription and Use After Cesarean Delivery," Obstetrics & Gynecology, vol. 130, no. 1, pp. 29-35, 2017.

[6] American Society of Plastic Surgeons, "2017 Cosmetic Plastic Surgery Statistics," 2017. [Online]. Available: https://www.plasticsurgery.org/documents/News/Statistics/2017/plastic-surgerystatistics-report-2017.pdf. [Accessed 2 January 2019].

[7] van Elk, Niek et al.;, "Chronic pain in women after breast augmentation: Prevalence, predictive factors and quality of life," European Journal of Pain, vol. 13, pp. 660-661, 2009.

[8] von Sperling, ML et al., "Persistent pain and sensory changes following cosmetic breast augmentation.," European Journal of Pain, vol. 15, no. 3, pp. 328-332, 2012.

[9] Cumon, Roberto et al.;, "Postsurgical Pain Related to Breast Implant: Reduction with Lipofilling Procedure," International Journal of Experimental and Clinical Pathophysiology and Drug Research, vol. 28, no. 5, pp. 993-996, 2014.

[10] Hart, Alexandra M, M.D. et al.;, "Opioid Use following Outpatient Breast Surgery: Are Physicians Part of the Problem?," Plastic and Reconstructive Surgery, vol. 142, no. 3, pp. 611-620, 2018.

[11] 1.. Hsu E, Cohen SP, Postamputation pain: Epidemiology, mechanisms, and treatment: J Pain Res, 2013; 6; 121-36

[12] U.S. Department of Health and Human Services. (n.d.). *Next-Gen Device could relieve Phantom Limb pain*. National Institutes of Health. Retrieved January 9, 2023, from https://heal.nih.gov/news/stories/phantom-limb-pain

[13] Ziegler-Graham K, MacKenzie EJ, Ephraim PL, Travison TG, Brookmeyer R. Estimating the prevalence of limb loss in the United States: 2005 to 2050. *Arch Phys Med Rehabil*. 2008;89(3):422-429. doi:10.1016/j.apmr.2007.11.005

[14] Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. *BMJ Open.* 2012;2:e000435