

Percutaneous Peripheral Nerve Stimulation to Control Postoperative Pain, Decrease Opioid Use, and Accelerate Functional Recovery Following Orthopedic Trauma

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ABSTRACT Orthopedic trauma is a significant military problem, causing several of the most disabling conditions with high rates of separation from duty and erosion of military readiness. The objective of this report is to summarize the findings of case series of a non-opioid therapy—percutaneous peripheral nerve stimulation (PNS) – and describe its potential for postoperative analgesia, early opioid cessation, and improved function following orthopedic trauma. Percutaneous PNS has been evaluated for the treatment of multiple types of pain, including two case series on postoperative pain following total knee replacement ($n = 10$ and 8 , respectively) and a case series on postamputation pain ($n = 9$). The orthopedic trauma induced during TKR is highly representative of multiple types of orthopedic trauma sustained by Service members and frequently produces intense, prolonged postoperative pain and extended opioid use following surgery. Collectively, the results of these three clinical studies demonstrated that percutaneous PNS can provide substantial pain relief, reduce opioid use, and improve function. These outcomes suggest that there is substantial potential for the use of percutaneous PNS following orthopedic trauma.

INTRODUCTION

Orthopedic trauma is a significant problem in the military and Veteran populations, causing several of the most disabling conditions that contribute to separation from duty (e.g., post-traumatic osteoarthritis (OA), joint replacement, amputation).¹ Combat-related extremity injuries in particular have been associated with increased inpatient stays and a majority of findings of “unfit for duty,” with estimated disability costs near \$2 billion.² Traumatic injuries (e.g., high-energy injuries; blunt/penetrating/perforating trauma) may involve damage of multiple tissue types, including skin, muscle, bone, joint, and nerve (Figs 1,2). While injuries caused by orthopedic trauma can cause considerable pain, the surgeries to treat orthopedic trauma can also cause substantial long-lasting postoperative pain. Postoperative pain following orthopedic surgeries such as bone fracture repair, amputation, limb salvage, and joint

replacement, is moderate to severe in up to 90% of patients, and uncontrolled acute postoperative pain can transition to chronic pain, frequently lasting multiple years.^{3–5}

Following orthopedic surgery, pain is a primary source of disability that inhibits rehabilitation, limits a return to normal function, and correlates negatively with return to duty or employment.^{6–8} Poor function following major orthopedic surgery can persist for ≥ 1 years in 25–50% of patients, resulting in high rates of medical separation from military service and failure to return to work.^{9–12} An inability to participate effectively in rehabilitation after trauma or surgery due to pain can lead to volumetric muscle loss, a disqualifying problem that further prevents return to duty.¹³

One of the primary treatments for postoperative pain is opioids, which can result in misuse, addiction, and debilitating side effects that often interfere with function, activities of daily living, and physical rehabilitation.¹⁴ In addition, patients who undergo the most painful orthopedic surgeries often use opioids for several weeks following surgery.^{15–17} Such long-term use of opioids increases the risks of addiction, dependence, use of illicit substances (e.g., heroin), overdose, and death.^{14,18}

Anesthetic nerve blocks can provide postoperative pain relief while recovering from surgery in the hospital, but they are not compatible with extended use outside of the hospital. Analgesia from injections last ≤ 24 hours and cannot be delivered outside the clinical setting. Continuous nerve blocks are seldom used for more than 4–7 days due to the risk of catheter dislodgement and infection.^{19,20} Nerve blocks also carry the risk of muscle weakness and reduced proprioception due to inadvertent block of motor and sensory fibers that increase the risk of falling.

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Traditional methods of electrical stimulation avoid some complications of medications and nerve blocks and have been used successfully to treat chronic pain. However, traditional methods of stimulation (e.g., spinal cord stimulation) require invasive surgery to implant the permanent electrodes and stimulator. As a result, they are not practical as a temporary postoperative therapy. The objective of the present report is to describe the use of a novel modality of neurostimulation – percutaneous peripheral nerve stimulation (PNS) – for postoperative analgesia in orthopedic indications that are common in military and Veteran populations.

METHODS

Percutaneous Peripheral Nerve Stimulation

Percutaneous PNS utilizes a fine wire open-coil stimulation lead temporarily implanted percutaneously to target peripheral nerves that innervate the region of pain. The lead is connected to an external stimulator, and the therapy is designed to deliver selective stimulation of pain-relieving fibers to avoid the induction of unwanted muscle contractions, muscle weakness, and reduced proprioception.

Percutaneous PNS has received United States (U.S.) Food and Drug Administration (FDA) 510(k) clearance for the treatment of chronic pain and acute pain, including postoperative and post-traumatic pain, for up to 60 days in the back and/or extremities (SPRINT PNS System, SPR Therapeutics, Inc, Cleveland, OH, USA). The lead is designed to remain indwelling for an extended duration with minimal risk of infection and lead migration. The leads consist of a 0.1-mm diameter, 7-strand stainless steel wire insulated with a fluoropolymer and wound into an open helical coil with the distal tip forming an anchor (Fig. 3). The lead is preloaded into a 20-gauge needle and implanted percutaneously using ultrasound guidance towards the target nerve, leveraging approaches similar to those used for local anesthetic injections and other ultrasound-guided procedures. For example, when used to treat lower limb pain, the lead may be implanted near the femoral crease to target the femoral nerve. Similarly, a lead may target the sciatic nerve using an approach similar to one used for local anesthetic-based sciatic nerve blocks (e.g., transgluteal). After the introducer is withdrawn and the lead is deployed, it is connected to an external stimulator (Fig. 4).

Device-related adverse events in clinical studies have been consistently mild (95%) or moderate (5%), anticipated, non-serious, and have required little to no intervention to resolve. The most common adverse events were limited to skin irritation, erythema, a blister, or a mild skin tear.^{21–28}

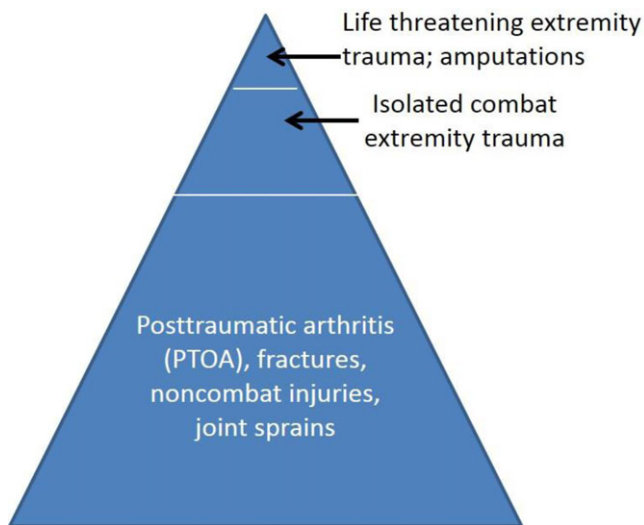


FIGURE 1. The “iceberg” of orthopedic injuries (adapted from Owens and Cameron).⁶⁸ The severe orthopedic traumatic injuries at the “tip” (e.g., amputation) receive a large share of attention from the media, researchers, and funding sources. Orthopedic injuries at the “base” receive less attention but cause a larger burden of injury and disease on the military and its health system. This is due in part to the surgeries to correct the injuries (e.g., joint replacement), which often induce trauma to soft tissue and bone and result in severe postoperative pain, prolonged opioid use, and delayed functional recovery.

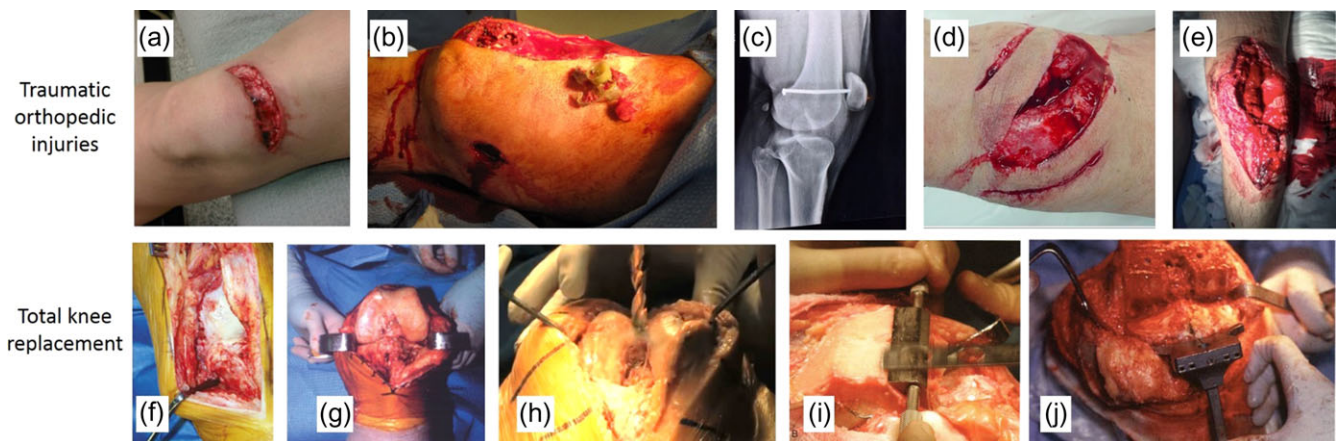


FIGURE 2. Traumatic orthopedic injuries and total knee replacements result in trauma to soft tissue and bone. Top: traumatic injuries, including (A) lacerations,⁷⁰ (B) shotgun blast injury,⁷¹ (C) nail through femur and patella,⁷² and (D, E) open knee fractures.^{73,74} Bottom: total knee replacement: (F) cut through soft tissue (i.e., skin, muscle, ligaments) to expose bone.⁷⁵ (G) Joint exposed by severing ligaments/meniscus.⁷⁵ (H–I) Drilling and sawing through bone.^{76,77} (J) Flat surfaces cut in bone and holes drilled through bone in preparation for joint implant.⁷⁷



FIGURE 3. A small-diameter (<math><0.3\text{ mm}</math>) open-coiled, helical electrical lead with an anchoring wire (MicroLead, SPR Therapeutics, Inc, Cleveland, OH, USA; figure used with permission from SPR Therapeutics).



FIGURE 4. A stimulator attached to the surface return electrode (SPR Therapeutics, Inc., Cleveland, OH, USA; figure used with permission from SPR Therapeutics).

No infections have been reported to date in over 330 leads when used to treat pain and left indwelling for up to 60 days (compared to 1.5% with continuous nerve block catheters), and the lead has a risk of infection of less than 1 per 30,000 indwelling days.^{20,29} Removal of the lead at the end of therapy does not require surgery and is performed similar to the removal of a continuous nerve block catheter. In addition, several hundred similar open-coil leads have been used safely in other non-pain indications^{30–33}, creating an established safety profile for the open-coil lead.

Evaluation of Percutaneous PNS in a Proxy Population That Is Highly Representative of Multiple Types of Orthopedic Trauma Sustained by Service Members

To prepare for major military conflicts that would be expected to produce a large volume of traumatic combat-related orthopedic injuries, studies of postoperative pain treatments should be conducted in patients that have experienced orthopedic trauma. However, orthopedic trauma presents unique challenges in clinical investigations due to a high degree of patient variability. Certain types of orthopedic trauma cause unpredictable severity and location of injury (e.g., high-energy injuries); confounding secondary health issues (e.g., compartment syndrome, infection); and variability in the degree of postoperative pain, opioid use, and disability.^{17,34,35} Also, surgeries must often be performed immediately following orthopedic trauma to stabilize the injury and save life or limb^{36–38}, and enrollment of this patient population into clinical studies is often

challenging (e.g., unpredictable surgery date, obtaining informed consent in vulnerable population, low/variable numbers of patients with combat-related trauma available prior to major military conflicts).

To address these issues, percutaneous PNS has been investigated in a well-defined proxy population representing the major characteristics of the target military population with traumatic orthopedic injuries. The proxy population consisted of individuals scheduled to undergo total knee replacement (TKR). While TKR has a high long-term success rate, it has a high incidence of long-lasting severe postoperative pain, extended opioid use (i.e., median time to opioid cessation of 45–60 days), and prolonged rehabilitation.^{15,16,35,39–43} Although joint replacements are used to correct joint damage (e.g., degeneration, injury), the surgeries themselves involve major injury to the joint and surrounding tissue to remove and replace the joint. TKR requires an incision through soft tissue and drilling and sawing through major weight-bearing bones, with potential for injury of other tissues and connective structures (Fig. 2). Unlike combat-related trauma, TKR induces orthopedic trauma in a predictable (controlled) manner, which is expected to reduce variability across study participants.

Functional recovery following TKR is often slow and impacted by postoperative pain. Patients who can undergo early and intense rehabilitation can minimize volumetric muscle loss and knee stiffness that typically occur following TKR, resulting in greater long-term functional outcomes.^{44–49} However, physical rehabilitation is delayed and greatly limited by both existing pain and the fear of inducing additional pain, which impedes recovery.^{45,50} As a result, it is common for activities of daily living to remain difficult and painful for a year or more following surgery^{9,10,45}, and one-third of the general population fail to return to work after joint replacement.⁵¹ These challenges associated with postoperative recovery following TKR are comparable or worse compared to other surgeries for orthopedic trauma.

Unlike combat-related trauma or orthopedic injuries following accidents, TKR is an elective procedure with a predictable surgery date scheduled weeks in advance, which facilitates enrollment, provides patients adequate time to consider their participation in the study, and allows for informed consent. Also, the high volume of TKR procedures suggests that the proxy population will be large (>700,000 TKR procedures per year in the USA).⁵²

In addition, joint replacement surgeries are highly relevant to the military population. Pain and activity limitations following joint replacement surgery result in medical separation of approximately 18% of military Service members.⁵³ Long-lasting pain following joint replacement is correlated with younger age⁵⁴, indicating that Service members are at a higher risk of disability and failure to return to duty. In a study examining the disabling conditions of the U.S. Army before and during Operation Iraqi Freedom and Operation Enduring Freedom, only amputation and total joint replacement were in the top 10 orthopedic conditions associated

with the highest percent disability in both peacetime and war; and during war, total joint replacement was the single condition with the highest average percent disability.¹

Further, TKR and other joint replacement surgeries are used to treat OA, one of the most common and disabling orthopedic war injuries. OA is one of the leading unfitting conditions among Service members with orthopedic war injuries, and many of these cases can be associated with a traumatic initiating event that leads to post-traumatic OA (PTOA)^{55,56} (Fig. 1). OA affects millions of U.S. adults,⁵⁷ and Service members and Veterans have even higher rates of OA and report more activity limitations than the general population.^{58,59} As a result, orthopedic trauma and joint replacement place a large burden on the military and its health system. The following studies were conducted by authors of the present study to explore the possibility of treating postoperative pain, decreasing opioid use, and improving functional recovery following orthopedic trauma using percutaneous PNS.

RESULTS

Three case series studies were conducted investigating the use of percutaneous PNS following orthopedic trauma (total *n* = 27). In Series 1, 10 individuals experiencing postoperative pain following surgically-induced orthopedic trauma (i.e., TKR) enrolled in a case series study.^{22,23} Six subjects were tested <14 days following surgery (range: 6–13 days), and the other four subjects were tested >40 days following surgery (range: 41–97 days). Fine-wire percutaneous leads were placed using ultrasound guidance to target the femoral and/or sciatic nerves. The leads were connected to external stimulators, and stimulation parameters were programmed to generate comfortable sensations in the regions of pain. Stimulation immediately reduced pain at rest compared to stimulation off by ≥50% in 9 subjects (90%) with an average reduction of 75%, and 5 subjects (50%) experienced complete pain relief. Stimulation did not subjectively impair motor function, and subjects were able to flex their knee without assistance. After

testing, all leads were removed safely, and no serious device-related adverse events were reported.

A second prospective case series study was conducted evaluating percutaneous PNS for postoperative analgesia after TKR (Series 2).⁶⁰ Eight individuals scheduled to undergo primary unilateral TKR enrolled at a single site (University of California, San Diego). Percutaneous leads were placed prior to surgery using ultrasound guidance to target the femoral and sciatic nerves. The leads were connected to external stimulators, and stimulation parameters were programmed to generate comfortable sensations in the region anticipated to be painful following surgery (i.e., knee and surrounding regions). Immediately prior to surgery, the leads were disconnected from the stimulators. A single-injection adductor canal block was administered (ropivacaine 0.5% and epinephrine; 20 mL), and spinal or general anesthetic was used to provide surgical anesthesia. Within 20 hours after TKR, stimulators were reconnected to the leads and turned on. During and following hospital discharge, subjects continued using stimulation for up to 6 weeks. There were no reports of impaired sensory/motor function during stimulation, and subjects were able to use stimulation during physical therapy and daily activities. The leads were left indwelling for a median duration of 45 days (range: 8–51 days) and removed at end of therapy. No falls, motor block, lead infections, or other serious device-related adverse events were reported.

Most subjects had well-controlled postoperative pain with percutaneous PNS following TKR. Subjects recorded their average daily pain in a diary using a 0–10 numerical rating scale. The average of daily pain scores for pain at rest, while walking, and overall was mild (<4/10)⁶¹ in a majority of subjects during the first week (Fig. 5). Average pain over the previous week was also assessed and was well-controlled during subsequent weeks; and, by 12 weeks following TKR, 7 of 8 subjects (88%) had well-controlled pain, and 5 subjects (63%) were pain free (Fig. 6). Four of the 8 subjects had well-controlled pain and discontinued opioid use within one week. The median time to opioid cessation across all 8 subjects was 16.5 days.

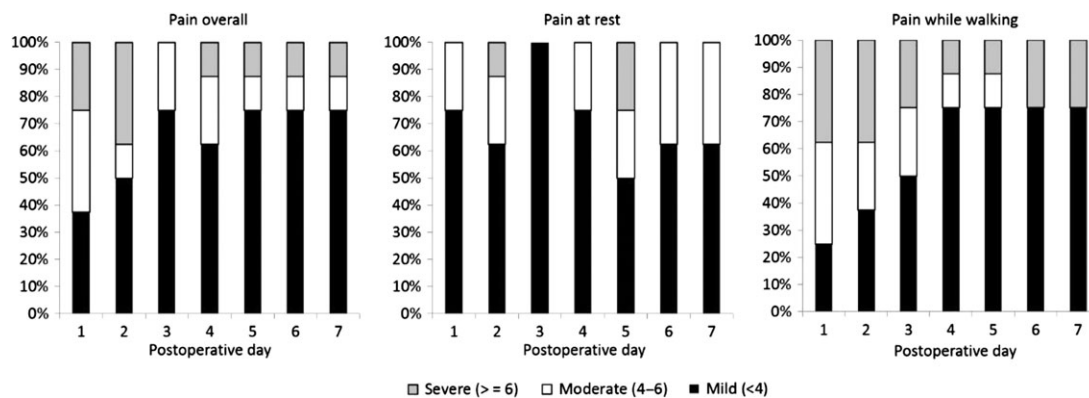


FIGURE 5. Percentage of subjects (*n* = 8) with mild, moderate, and severe postoperative pain (“Average pain over the last 24 hours”) overall [left], at rest [center], and during ambulation [right] through postoperative day 7 (Series 2).

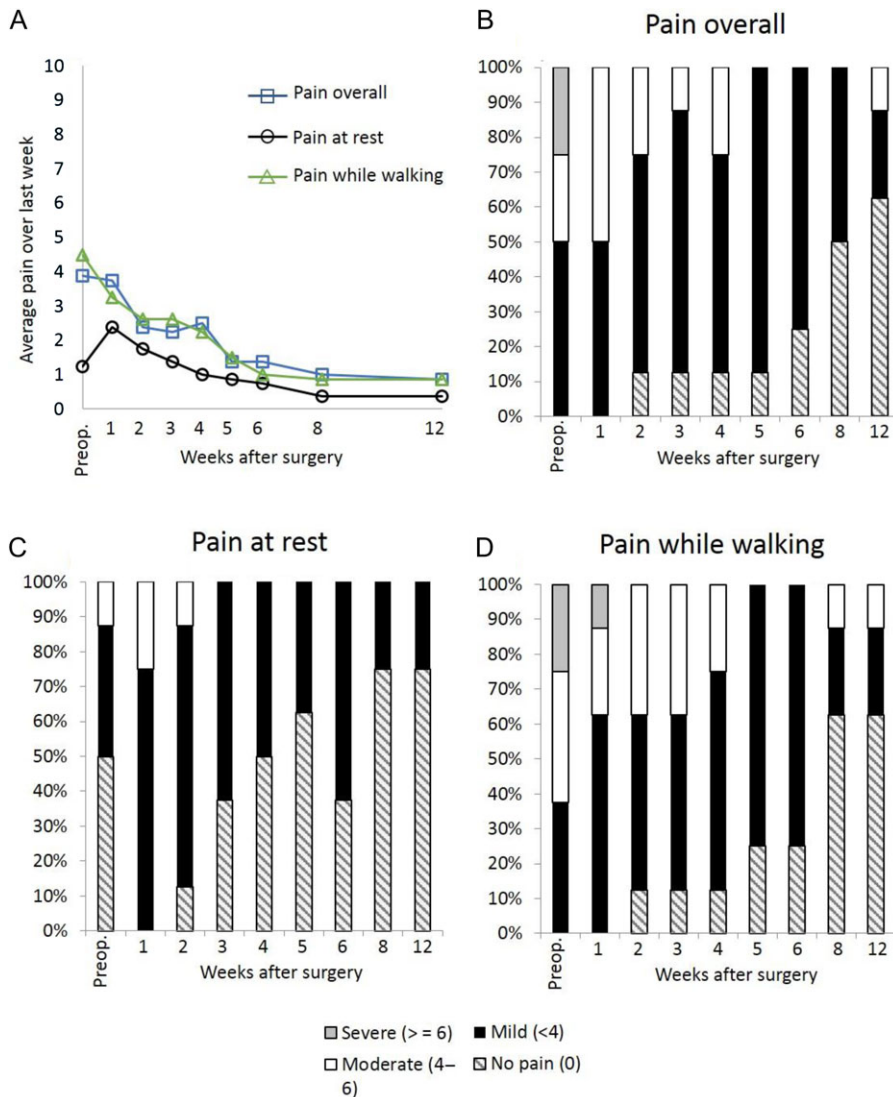


FIGURE 6. Average pain over the past week. Panel (A) Pain averaged across subjects ($n = 8$). Panels (B–D) Percentage of subjects with no pain, mild pain, moderate pain, and severe pain (B) overall, (C) at rest, and (D) while walking (Series 2).

Walking speed and endurance were assessed using the Six Minute Walk Test (6MWT), which measures the distance that a subject can walk in 6 minutes.⁶² All 8 subjects completed the 6MWT test preoperatively (average = 336 ± 56 m); and by 2 weeks following surgery, 6 of 7 subjects (86%) that were able to perform the 6MWT had returned approximately to preoperative levels ($\geq 95\%$ of preoperative distance) (average distance = 312 ± 87 m). By 12 weeks following surgery, 7 of 8 subjects (88%) had improved on the 6MWT by $\geq 10\%$ compared to preoperative distances (average distance = 410 ± 56 m), with an average improvement of 24%.

Functional outcomes improved following surgery compared to before surgery as measured by the Western Ontario & McMaster University Osteoarthritis Index (WOMAC; assesses pain, stiffness, and difficulty with activities of daily living). By 6 weeks following surgery, all 8 subjects (100%)

had achieved clinically significant improvements in WOMAC of at least 33%⁶³, with an average improvement of 76%. By 12 weeks following surgery, the average improvement relative to before surgery was 86%.

The results of this case series study compare favorably to studies described in the Methods reporting outcomes following TKR using standard techniques of postoperative analgesia (i.e., oral medications, local anesthetic-based nerve blocks). Recent studies showed that more than 80% of patients continued to use opioids at 2 weeks following TKR, more than 70% of patients continued to use opioids at 4 weeks following TKR, and the median time to opioid cessation was approximately 45–60 days.^{15,16,35,39,40} Also, published studies assessing the 6MWT at 1 year following surgery reported average distances across studies of only 116% compared to preoperative distances (i.e., 16% improvement; range = 99–130%).^{44–46,64–67} Comparisons to

historical controls from previous studies should be considered cautiously; nonetheless, the ability of percutaneous PNS to reduce opioid use and accelerate functional recovery following orthopedic surgery is promising.

Additionally, percutaneous PNS was investigated previously by some of the authors of the present study as a method to provide chronic pain relief in amputees.²¹ In a case series feasibility study (Series 3), nine subjects with lower limb amputations enrolled and received 2 weeks of stimulation. All subjects reported clinically significant⁶⁸ ($\geq 30\%$) reduction in pain at end of treatment (average reduction = 76%). Also, all 9 subjects reported improved function with an average of 82% reduction in pain interference on daily activities, including 4 (44%) subjects who reported 100% improvement (*i.e.*, no pain interference) at the end of the stimulation period.

CONCLUSIONS

Collectively, these prospective case series studies suggest that percutaneous PNS may relieve pain, reduce opioid use, and improve function following orthopedic trauma. The pain indications for which percutaneous PNS may benefit Service members, Veterans, their families, and other military health system beneficiaries include pain following the most severe orthopedic injuries (tip of the “iceberg”, Fig. 1) and the surgeries used to treat the most common orthopedic injuries that place an immense burden on the military and its health system (middle and base of “iceberg”, Fig. 1).⁶⁹ A limitation of these studies is the small sample sizes, and randomized controlled trials in patients following orthopedic trauma are in progress and are expected to further elucidate the relative risks and benefits of percutaneous PNS for postoperative pain.

PREVIOUS PRESENTATION

Presented as a poster at the 2017 Military Health System Research Symposium, Kissimmee, FL (abstract MHSRS-17-1450).

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