A Feasibility Study of Percutaneous Peripheral Nerve Stimulation for the Treatment of Postoperative Pain Following Total Knee Arthroplasty

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INTRODUCTION

Total knee arthroplasty (TKA) is among the most common surgical procedures (1,2). Following TKA, patients commonly experience prolonged moderate-to-severe postoperative pain, extended opioid use, and delayed functional recovery (3–5). Postoperative pain is most often treated with opioid analgesics; however, these have a high risk of misuse and debilitating side effects (e.g., sedation, dizziness, nausea, constipation, urinary retention, and sleeping problems) that often interfere with physical rehabilitation and function. Recent studies show that opioid use continues at least four weeks following TKA in over 70% of patients, with the median time to opioid cessation approximately 45–60 days (4,6,7).

Peripheral nerve blocks provide effective postoperative analgesia during hospitalization (8). However, single-injection blocks (e.g., femoral nerve block, adductor canal block) provide analgesia for less than a day; while continuous peripheral nerve blocks are rarely used for greater than a few days or following discharge due to the inconvenience of carrying a portable infusion pump and local anesthetic reservoir, the relatively rapid consumption of local anesthesia, as well as the risks of infection and catheter dislodgement (8). In addition, peripheral nerve blocks often induce sensory, motor, and proprioception deficits, which may potentially interfere with physical rehabilitation and possibly increase the risk of falls (9,10).

Percutaneous peripheral nerve stimulation (PNS) is a non-opioid pain treatment that delivers electrical stimulation to peripheral nerve fibers through a percutaneous lead connected to an external pulse generator. Previous studies have demonstrated the safety and effectiveness of percutaneous PNS for the treatment of various chronic pain conditions, including low back pain, neuropathic pain (e.g., phantom limb pain and residual limb pain), and shoulder pain (11–22). Recent studies suggest that percutaneous PNS can produce immediate reductions in postoperative pain following TKA in a brief (single day) in-office test more than a week following surgery: 9 out of 10 subjects (90%) experienced >50% pain relief, and the average pain relief was 75% with stimulation compared to baseline (23,24). The primary aim of this prospective feasibility study was to determine if using percutaneous PNS is feasible in the immediate perioperative period following TKA (25). The secondary aims of the study were to investigate the analgesic, opioid sparing potential, and impact on functional recovery of percutaneous PNS following TKA relative to published averages, as well as to produce data to help power a subsequent randomized, controlled clinical trial.

METHODS

This prospective feasibility study was approved by the Food and Drug Administration (FDA) under an investigational device exemption (IDE) and the University of California San Diego Institutional Review Board (IRB). The study was prospectively registered with ClinicalTrials.gov (NCT02468934). Subjects were enrolled in the study after providing written, informed consent and meeting all inclusion/exclusion criteria. Inclusion criteria included being scheduled to undergo primary, unilateral TKA and at least 21 years of age. Exclusion criteria included body mass index greater than 40 kg/m²; increased risk of infection (e.g., compromised immune system, history of valvular heart disease, history of skin infections; evidence of joint or overlying skin infection of the affected limb); implanted cardiac pacemaker/defibrillator or deep brain stimulator; increased risk of excessive bleeding (i.e., bleeding disorder, INR ≥ 1.5 for patients on warfarin); comorbidity affecting the ipsilateral leg (e.g., radiculopathy, fibromyalgia, and central nervous system disorder); allergy to skin surface electrodes or medical grade adhesives; and pregnancy.

Subjects received percutaneous PNS systems (SPRINT™ PNS System, SPR Therapeutics, Inc., Cleveland, OH, USA) that have since been FDA cleared for up to 60 days for the treatment of chronic pain and acute pain, including post-traumatic and postoperative pain. The system includes a percutaneous lead (MicroLead; SPR Therapeutics) that is 0.2 mm in diameter and has an open-coil design (Fig. 1) intended to resist infection (<0.1% infection rate when used for up to 60 days) (26). Each lead was preloaded in a 20-gauge introducer needle and inserted percutaneously using ultrasound guidance up to seven days prior to TKA to deliver PNS to the femoral and sciatic nerves. One lead was inserted near the femoral crease of the leg ipsilateral to the knee undergoing TKA using an ultrasound guidance system, and a second lead was inserted using ultrasound guidance up to 10–30 mm from the sciatic nerve. Each lead was connected to an external pulse generator to evoke comfortable sensations in the regions surrounding the knee. Stimulation was delivered at 100 Hz with amplitude up to 20 mA and pulse duration up to 200 μs. For subjects who underwent lead placement more than two days prior to TKA, stimulation was delivered continuously until the day of surgery with the exception of showering.

Figure 1. A small-diameter (0.2 mm) open-coiled, helical electrical lead with an anchoring wire (MicroLead; SPR Therapeutics, Inc., Cleveland, OH, USA; figure used with permission from SPR Therapeutics).
Immediately prior to surgery, the leads were disconnected from the external pulse generators and secured beneath sterile bandages. A single-injection adductor canal block was administered under ultrasound guidance with ropivacaine 0.5% and epinephrine (20 mL) (27). Spinal or general anesthetic was used to provide surgical anesthesia. Within 20 h after TKA surgery, stimulators were reconnected to the leads and turned on. Subjects were instructed to use stimulation continuously during and following hospital discharge (i.e., 24 h per day except when showering and during battery changes), and subjects continued using stimulation for up to a total of six weeks, after which the leads were removed by an investigator using gentle traction.

Outcomes

Average pain at rest, while walking, and overall were each measured using the 0–10 numerical rating scale of the Brief Pain Inventory-Short Form, Question 5 (BPI-5). Pain scores over the previous 24 h were assessed daily during the percutaneous PNS therapy using a diary. Pain over the previous week was also assessed verbally during phone calls or visits weekly, and these pain scores were used to replace missing pain scores in the diary from the previous week. Pain at rest, while walking, and overall was mild (<4 out of 10 on BPI-5) (35) in six of seven subjects (86%) (Fig. 2). Pain continued to be well controlled and mild for six of seven subjects at weeks 2, 3, and 4 as well.

Four of the seven subjects (57%) had well controlled and mild pain and had discontinued opioid use within the first week (Figs. 3 and 4). One of the four subjects did not use opioids during the entire therapy, while the other three subjects discontinued opioid use on postoperative days 4, 4, and 6. The median time to opioid cessation across all seven subjects was six days (Table 2).

Subjects had returned approximately to preoperative walking levels on both the TUG test and 6MWT by two weeks following TKA (Table 3). All seven subjects completed the TUG test preoperatively (average = 13.9 ± 1.5 s). Six of the seven subjects were administered the TUG test on the day of discharge from the hospital following TKA (subject 3 was discharged early on POD 1 before the TUG test could be administered). Of these six subjects, all 6 (100%) were able to complete the test (average = 34.9 ± 10.7 s). Two weeks following surgery, five of the seven subjects (71%) had returned approximately to preoperative levels or better on the TUG test (within 5% of preoperative times) (average = 13.6 ± 4.3 s). Also, all seven subjects completed the 6MWT test preoperatively (average = 323 ± 46 m); and by two weeks following surgery, six of seven subjects (86%) had returned approximately to preoperative levels (≥ 95% of preoperative distance) (average distance = 311 ± 88 m). By 12 weeks following surgery, six of seven subjects had improved on the 6MWT by at least 10% compared to preoperative distances (average distance = 402 ± 55 m), with an average improvement of 26%.

Functional outcomes improved following surgery compared to before surgery as measured by the WOMAC questionnaire (Table 4).

### Table 1. Patient characteristics.

| Subject # | Age (years) | Sex | Knee | Height (cm) | Weight (kg) |
|-----------|-------------|-----|------|-------------|-------------|
| 1         | 63          | Male| Left | 188         | 109         |
| 2         | 77          | Male| Left | 175         | 84          |
| 3         | 72          | Male| Right| 178         | 82          |
| 4         | 66          | Female| Right| 152         | 94          |
| 5         | 71          | Female| Left | 165         | 83          |
| 6         | 74          | Female| Right| 165         | 73          |
| 7         | 51          | Female| Left | 165         | 88          |

### Table 2. Days of opioid discontinuation and lead removal.

| Subject # | Postoperative day of opioid discontinuation | Postoperative day of lead removal | Reason for lead removal |
|-----------|--------------------------------------------|----------------------------------|-------------------------|
| 1         | 48                                         | 8                                | Adverse event unrelated to device; only mild pain at time of lead removal |
| 2         | 65                                         | 43                               | End of treatment period |
| 3         | 4                                         | 8                                | Discomfort during stimulation; only mild pain at time of lead removal |
| 4         | 29                                         | 47                               | End of treatment period |
| 5         | 0                                          | 42                               | No pain or opioid use |
| 6         | 4                                          | 32                               | End of treatment period |
| 7         | 6                                          | 38                               | End of treatment period |
At two weeks following TKA, WOMAC scores improved by an average of 46% compared to before surgery, with five of seven subjects (71%) achieving a clinically significant improvement of ≥33%. By 12 weeks following surgery, the average improvement relative to before surgery was 85%, and all seven subjects (100%) had achieved clinically significant improvements in WOMAC (36–38).

No falls, motor block, lead infections, or other serious device-related adverse events were reported. One subject experienced discomfort at the site of the surface return electrode (a non-serious, anticipated adverse event), which resolved following lead removal without additional treatment. One subject experienced headaches, the cause of which could not be determined. One of 14 leads (7%) was dislodged inadvertently during therapy. Four of the seven subjects (Subjects 2, 4, 5, and 7) had leads removed as planned at approximately six weeks following TKA. The other three subjects (subjects 1, 3, and 6) underwent lead removal early on postoperative day 8, 8, and 32, respectively; and, the three subjects all had mild pain (BPI-5 = 2, 3, and 0, respectively) at time of lead removal (Table 2). Across the seven subjects, 3 of 14 leads (21%) fractured during intentional extraction. The fragments were left in situ and did not produce subsequent complications.

DISCUSSION

The present study investigated the feasibility of using perioperative percutaneous PNS, a novel treatment for postoperative pain that enables prolonged non-opioid therapy both during and many weeks following hospital discharge. The results suggest that PNS may provide well-controlled postoperative pain and enable early opioid cessation, as well as an accelerated return to function following TKA.
Previous studies on outcomes following TKA using traditional approaches to postoperative analgesia have reported extended opioid use and delayed functional recovery. In recent studies of patients receiving various postoperative treatments (e.g., oral medications, local anesthetic-based nerve blocks, transcutaneous electrical nerve stimulation, intravenous acetaminophen), average opioid consumption is often greatest during the immediate postoperative period (e.g., average daily morphine equivalent dosage [MED] of approximately 30–170 mg during postoperative days 0–3) (7, 39–43); fewer than 30% of patients had ceased opioid use by four weeks following TKA, and the median time to opioid cessation was approximately 45–60 days (4, 6, 7). In the present study, average daily MED during postoperative days 0–3 was approximately 22 mg, a majority (4 of 7; 57%) of subjects reported opioid cessation within the first week following surgery, and the median time to opioid cessation was six days. Also, a recent study examining opioid use in over 24,000 patients that had undergone TKA showed that the median total MED during the first 90 days following surgery was 370 mg, and less than 30% of patients had ceased opioid use by four weeks following surgery (average distance = 97% of preoperative distance; 6 of 7 subjects had returned to at least 95% of preoperative distances), and improved on average to 126% of preoperative distances by 12 weeks following surgery. While direct comparisons of previous studies to the present results must be considered cautiously, the outcomes of the present study are nonetheless promising and demonstrate the potential of percutaneous PNS to reduce opioid use and accelerate functional recovery following TKA.

Traditional neurostimulation systems have been used primarily for the treatment of chronic pain. Their use in treating non-chronic (i.e., acute, subacute) postoperative pain has been greatly limited due to the need for permanently implanted devices (e.g., pulse generator/stimulator, electrode/lead) requiring invasive surgery for implantation, removal, and revision if necessary (e.g., to correct lead migration or failure) (52–59). Percutaneous PNS avoids many of the drawbacks of traditional neurostimulation systems, requiring only a minimally invasive procedure (no incisions) to place the lead that makes it practical for perioperative use.

Table 3. Mobility tests.

| Subject # | Prior to surgery | TUG Test (s) | Prior to surgery | 6MWT (m) |
|-----------|------------------|-------------|------------------|---------|
|           | Day of discharge | 2 weeks after surgery | Day of discharge | 6 weeks after surgery |
| 1         | 13               | 22          | 15               | 300     |
| 2         | 16               | 52          | 16               | 303     |
| 3         | 14               | a           | 12               | 408     |
| 4         | 14               | 30          | 14               | 303     |
| 5         | 11               | 40          | 21               | 343     |
| 6         | 14               | 39          | 7                | 343     |
| 7         | 15               | 28          | 10               | 266     |
| Mean      | 14               | 35          | 14               | 324     |
| SD        | 2                | 11          | 4                | 46      |

| aNot assessed: subject was discharged early from hospital before TUG could be assessed.

Table 4. Raw average scores and percentage improvement from baseline as measured with the WOMAC.

| Subject # | Prior to surgery | 2 weeks after surgery | 6 weeks after surgery | 12 weeks after surgery |
|-----------|------------------|-----------------------|-----------------------|-----------------------|
| 1         | 1.8              | 2.3                   | −27%                  | 0.5                   |
| 2         | 2.3              | 2.0                   | 11%                   | 0.8                   |
| 3         | 2.6              | 1.1                   | 59%                   | 0.2                   |
| 4         | 3.5              | 2.1                   | 41%                   | 0.7                   |
| 5         | 4.9              | 2.0                   | 59%                   | 1.5                   |
| 6         | 4.6              | 0.3                   | 94%                   | 0.2                   |
| 7         | 7.1              | 1.2                   | 83%                   | 0.0                   |
| Mean      | 3.8              | 1.6                   | 46%                   | 0.7                   |
| SD        | 1.9              | 0.7                   | 39%                   | 0.5                   |

Each question was assessed on a 0–10 numeric rating scale, with lower scores indicating improved function. Positive values of percentage change indicate improvement from pre-operative baseline.
316L stainless steel wire wound into an open helical coil with a single anchor at the tip (Fig. 1). Its small size enables percutaneous insertion of the lead using a 20-gauge needle and non-surgical removal with traction. The helical design helps keep the lead from moving by bending and stretching when subjected to force and encourages tissue ingrowth between the coils to secure the lead in place. These features theoretically decrease lead migration (which can cause discomfort and/or reduced analgesia) and reduce the risk of infection to 0.03 per 1000 indwelling days. No infections have been reported to date in over 330 lead placements when used to treat pain and left indwelling for up to 60 days (26). No complications were reported due to lead fragments retained upon lead removal (3 of 14 leads). The lack of infectious and neurologic complications is consistent with previous studies of percutaneous PNS for the treatment of pain, where a lower rate of lead fracture has been reported (11,12,14–24). Also, a recent study evaluating potential MRI related issues of retained fragments of the open-coil lead demonstrated that retained lead fragments are MR Conditional at 1.5 Tesla with whole body averaged specific absorption rate (SAR) of 2 W/kg (i.e., with the MR system operating in the Normal Operating Mode) for 15 min of scanning per pulse sequence; at 3 Tesla, lead fragments passed safety testing for artifacts and magnetic field interactions (i.e., translation and torque), and all tested fragments exhibited physiologically inconsequential heating. While additional testing is needed to evaluate heating for fragments >11.2 cm in length, lead fractures that have occurred with this system have been shorter in length and most lead fractures that have been observed have occurred at or near the distal tip (<1.5 cm) (60).

Relatively recent developments may enable percutaneous PNS to become widely adopted for the treatment of post-surgical pain. The broad availability of ultrasound machines and anesthesiologists trained in ultrasound-guided regional anesthesia suggests that the proper equipment and training are already in place in most centers to implement this therapy. Also, the percutaneous PNS system used in the present study received U.S. FDA 510(k) clearance for the treatment of chronic pain and acute pain, including postoperative and post-traumatic pain.

An important limitation of the current prospective feasibility study design is a lack of a control group as well as the small size of the study (n = 7). Using the data of the current series, future studies will be designed and conducted to further investigate the relative risks and benefits of percutaneous PNS for the treatment of postoperative pain.

Conclusions

This prospective feasibility study suggests that periproperative percutaneous PNS may enable reduced postoperative pain, earlier opioid cessation, and accelerated functional recovery following TKA.

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Authorship Statements

Dr. Ilfeld was responsible for the study design, data analysis, conducting and providing guidance on study procedures, substantial contributions to first draft of manuscript and review of subsequent drafts. Drs. Ball, Gabriel, Sztaín, Monahan, Abramson, Khatibi, Said and Parekh were responsible for conducting study procedures and reviewing the manuscript. Dr. Grant was responsible for the study design, data analysis and review of the manuscript. Dr. Wongsampongo was responsible for the study design, data analysis, investigator/coordinator training on protocol and use of stimulation system, substantial contributions to first draft of manuscript and review of subsequent drafts. Dr. Boggs was responsible for the study design, data analysis and review of the manuscript.

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