Short Communication

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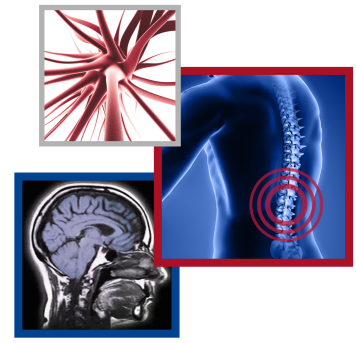

Prospective case series on the use of peripheral nerve stimulation for focal mononeuropathy treatment

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Practise points

- Over 100 million adults in USA experience chronic pain yet current treatment options are limited.
- Peripheral nerve stimulation, possibly through the release of inflammatory neurotransmitters and endorphins directly involved in the pain pathway, shows potential in increasing pain threshold for certain populations.
- Our 39-patient case series supports the use of neuromodulation treatment for mononeuropathy through improvement in visual analog scale pain scores and a decrease in opiate use and improvement in daily function.
- Further studies are necessary to support our conclusion that peripheral nerve stimulation may be a viable treatment option for focal mononeuropathy.

Aim: Thiscase series looks at outcomes in 39 patients implanted using the Bioness Stimrouter system on various isolated mononeuropathies. **Patients & methods:** A case series of 39 patients with a total of 42 implants were enrolled starting August 2017 at various pain management centers. **Results:** Of 39 patients studied, 78% of the participants noticed an improvement in their pain. There was a 71% reduction in pain scores with the average preprocedure score of 8 improving to 2 post-implant. Participants noted on average a 72% improvement in activity with the greatest observed in the brachial plexus (80%) and suprascapular nerve (80%) and smallest in the intercostal nerve (40%). Approximately 89% of those implanted with a peripheral nerve stimulator experienced a greater than 50% reduction in opioid consumption. **Conclusion:** Peripheral nerve stimulators are a new, minimally invasive neuromodulation modality that shows promising early results in our 39-patient case series.

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Keywords: case series • chronic pain • focal mononeuropathy • opioids • peripheral nerve stimulation

Approximately 10% of the US population experiences chronic neuropathic pain [1]. Despite its widespread prevalence, nerve pain remains difficult to treat. Current conservative treatments with anticonvulsants, capsaicin and antidepressants are marginally effective with less than 50% of the population experiencing a greater than 50% reduction in pain [2]. Short courses of opioids are effective in treating neuropathy and neuralgia in the intermediate treatment period (8 days to 8 weeks) but its long-term efficacy is unknown [3]. Long-standing use of opioids for chronic pain is associated with hyperalgesia [4,5], increased tolerance [6] and increased addiction potential [7]. With the push to move away from prescribing opiate therapy for chronic pain, researchers are developing alternative nonopioid modalities.

The emerging field of neuromodulation has been successful in treating neuropathic pain [8–10]. Neuropathy remains a common indication to place a spinal cord [11] or dorsal root ganglion (DRG) stimulator [8]. Peripheral nerve stimulation (PNS), first described in 1967 [12], has a similar mechanism of action to traditional spinal cord stimulation (SCS). It is theorized that overactivation of large sensory afferent nerve fibers decrease transmission of painful stimuli [13]. Despite evidence supporting PNS's efficacy in treating neuropathic pain [14–18], traditional SCS has been a more popular treatment modality. Other proposed mechanisms utilize the Frankenhauser–Huxley

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Table 1. Implant facility and total number of implants.

Implant facility	Number of implants
Stanford	8
Johns Hopkins Health System	1
Kerlan–Jobe Orthopaedic Clinic	2
Oklahoma Heath	1
The Surgical Center of Connecticut	8
Duke Pain Medicine	2
Spine Institute Northwest	3
The Premier Surgical Center New Jersey	1
Surgery Center Camelback	1
HolyCross	1
Surgery Center of Des Moines – East	1
Potomac View Surgery Center	1
Brigham and Women's Hospital	2
VCU/Virginia Commonwealth University Health System	1
Mount Sinai	1
University of Michigan	1
Alliance Surgery Center	1
Emory Acute Surgery Center	2

model suggesting the therapeutic mechanism of action is the association between the activation of potassium and inactivation of sodium channels involved in neuronal conduction block [19].

Up until recently, PNS implantation required surgical dissection with the direct placement of a multi-contact electrode (paddle) along or immediately adjacent to the nerve [20]. The open surgery was complicated by iatrogenic nerve injury [21,22] and a greater than 85% revision rate [23]. In 1999, Weiner *et al.* published favorable results of a percutaneously implanted PNS system for treatment of occipital neuralgia [24]. Subsequent work continued to support PNS percutaneous implantation as a safe and efficacious treatment for craniofacial [18] and extremity neuropathic pain [25]. One observed limitation with the first PNS devices was the size of the implantable pulse generator (IPG). It was difficult to find a peripheral pocket large enough for implantation and installation on the trunk requiring a long tunneling course.

Subsequently, a new peripheral nerve stimulator was designed for percutaneous placement with an external IPG. In their manuscript, Deer *et al.* describes a PNS system that is subcutaneously implanted with either fluoroscopy or ultrasound that uses a three-electrode contact with a four-pronged anchoring system. The device is powered and controlled by an external pulse generator that is mounted with adhesives to the skin adjacent to the PNS [26]. In his prospective, multicenter, randomized, double-blind, partial crossover study of 94 patients, Deer *et al.* demonstrated improvement of neuropathic pain pre- and postimplant of the novel PNS device [26].

With this new minimally invasive, percutaneous implantation technique, it seems logical to consider a potentially less invasive, peripheral neuromodulation device that directly targets the affected nerve. Since the published study by Deer *et al.,* there has been a shortage of recent evidence on the validation of PNS on treating focal mononeuropathy. The purpose of this study is to show the results from a 39-patient case series using a peripheral nerve stimulator in treating mononeuropathy. To our knowledge, this is one of the first studies of its kind describing the exact nerve location of a PNS implantation with an external pulse generator and its efficacy as well as length of time the disposable user patch was applied.

Patients & methods

A case series of 39 patients with a total of 42 implants were enrolled in a Bioness postimplant survey study starting in August 2017 at various pain management centers in USA. The centers that participated in the study are provided in Table 1, the nerve location, technique, number of implants and target nerve are provided in Table 2. There was a total of 39 participants and 42 PNS evaluated. One participant had a bilateral tibial nerve implant and two subjects had two PNS implanted on different nerves. Not all participants answered every question on the survey (see n-values on charts for responders). Patients were surveyed by Bioness before and approximately 3–6 months

Table 2. Summary of methodological parameters.

Implanted nerve	Indication	Number of responders	Diagnostic block prior to implant/total responders	Sedation used	Imaging technique	Single- or dual-incision closure
Axillary	Poststroke shoulder pain (6/13)	13	2/5	MAC with local (6/6)	US: 6; Fluoroscopy and US: 1; Unknown: 5	Dual: 8; Unknown: 5
Genital femoral	Genital femoral neuralgia	1	1/1	Unknown	US and paresthesia	Dual
Intercostal	Unknown	1	1/1	MAC	US	Dual
Ilioinguinal	Unknown	1	1/1	Unknown	US and paresthesia	Dual
Lateral femoral cutaneous	Unknown	3	2/3	Unknown	US and paresthesia: 2 Unknown: 1	Dual: 2; Unknown: 1
Peroneal	Unknown	2	1/2	MAC: 1; Unknown: 1	US: 1; Unknown 1	Dual: 1; Unknown: 1
Intercostal	Unknown	1	0/1	General	US	Dual
Saphenous	Unknown	2	1/2	Local: 1; MAC: 1	US: 2	Dual
Suprascapular	Unknown	1	1/1	Unknown	Paresthesia and US	Dual
Sural	Unknown	1	1/1	Unknown	Paresthesia and US	Dual
Tibial	Unknown	5	4/4	Local: 3; Unknown: 2	Paresthesia and US: 2 US: 3	Dual: 5

MAC: Monitored anesthesia care; US: Ultrasound.

after device implantation. A total of 54% of the patients surveyed were female and 46% were male. Data obtained from survey were analyzed and presented in this paper.

All patients who received a Bioness StimRouter PNS were included in the study with no exclusions. Indication for implantation was chronic mononeuropathic pain. Many of the patients in our survey failed conventional SCS, DRG and nerve ablative procedures. Due to our inability to present each individual technique used for each target nerve (>17 peripheral nerves targeted with Bioness Stimrouter), we have attempted to summarize the key elements of the procedural technique in Table 2 for the nerves targeted in our study. We recommend providers consult Bioness with regard to recommendations on specific techniques and reference guides for more detailed methodology. The majority of patients in our study received a preprocedure test block along the suspected nerve with a greater than 50% reduction in pain. Most peripheral nerves were accessed using ultrasound using an in-plane technique (Table 2). Implants were performed using light sedation and/or local anesthetic. After placement and before implantation, the device was stimulated at least three-times between 0.5 and 1.5 mA, and patient feedback was obtained to ensure the detected paresthesia mapped the distribution of pain. A dual incision technique was performed to secure and permanently bury the lead. All implants were adjusted using the following ranges, intensity: 1–30 mA; frequency: 0–200 Hz; phase duration: 70–500 ms. Adverse events were not directly evaluated in this study but no serious events including infection and lead migration were reported. Bioness had obtained patient consents for all survey participants in all of the centers as part of standard of care.

Results

Summary of patient demographic

The study demographic mainly consisted of US patients in pain centers nationally that participated in a postimplant survey without any exclusion criteria. The minimum age of implantation was 18, with 54% of study subjects being females and 46% of study subjects being males. The average age of female patients was 59, and the average age of the male patient was 61. There were 24 different peripheral nerve locations that were involved in our study, and all subjects were asked the same postimplant questions with regard to change in visual analog scale (VAS) score, activity and postoperative opioid consumption.

Changes in VAS score

The average percent reduction of VAS pain scores ranged from 29 to 100%, differing by the peripheral nerve stimulated. The average VAS prior to implantation was 8 compared with 2 after PNS implantation with a noted reduction of 71% (see Table 3). The greatest reduction in pain scores were seen in the lateral femoral cutaneous nerve with preimplant pain scores improving from an average of 8 to 0 (100% reduction in pain score) post

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Table 3. Average change in visual analog scale score by peripheral nerve stimulated.

Location	N	Visual analog scale prior to implant	Visual analog scale after implant	Change (%)
Total	39	8.2	2.4	70.8
Lateral femoral cutaneous	3	8.3	0.0	100.0
Genitofemoral	1	10.0	1.0	90.0
Ilioinguinal	1	10.0	1.0	90.0
Sural	1	8.0	2.0	75.0
Peroneal	3	9.0	2.3	74.1
Axillary nerve	18	8.0	2.4	70.1
Suprascapular	1	9.0	3.0	66.7
Saphenous	3	7.7	2.7	65.2
Tibial	5	7.8	2.6	66.7
Brachial plexus	2	9.5	4.5	52.6
Intercostal	1	7.0	5.0	28.6

Table 4. Percent improvement in activity by peripheral nerve stimulated.

Nerve location	n	Improvement in activity (%)
Total	27	72.0
Axillary	14	73.5
Brachial plexus	1	80.0
Genitofemoral	1	75.0
Ilioinguinal	1	75.0
Intercostal	1	40.0
Lateral femoral cutaneous	2	70.0
Peroneal	2	75.0
Suprascapular	1	80.0
Sural	1	60.0
Tibial	3	73.3

implantation. The smallest pain score improvement (29%) was seen when PNS was implanted into the intercostal nerve with (n = 1).

Effect on activity

Data from all 27 participants who responded to the survey referring to improvement in activity stratified by the peripheral nerve involved are indicated in Table 4. Participants were asked to estimate their percent improvement in activity. All (100%) of the questionnaire responders noted improvement in activity with the quantification of their improvement ranging from 40 to 80%. Participants noted on average a 72% improvement in activity with the greatest noted in the brachial plexus (80%) and suprascapular nerve (80%) and smallest in the intercostal nerve (40%).

Table 5 indicates the duration in days the external pulse transmitter and disposable patch were applied prior to replacement. From the 34 total responders, the PNS was turned on 6.0 days per week requiring patch replacement every 5.2 days. Most of the data were available for responders with an axillary PNS who indicated using the PNS on average of 6.2 days per week requiring patch replacement every 4.4 days.

Effect of opioid consumption

Approximately 65% of the participants (11 of the 34 responders) were on opiates prior to PNS implantation. After implantation, participants noted an average reduction in opioid use by 68%. Figure 1 demonstrates that 89% of those implanted with a peripheral nerve stimulator observed a greater than 50% reduction in opioid consumption.

Table 5. Duration in days of external pulse transmitter and disposable patch application prior to replacement with new patch by peripheral nerve stimulated.

Nerve location	n	Average days Pt used device	Frequency of disposable patch replacement (in days)
Total	34	6.0	5.2
Axillary	16	6.2	4.4
Brachial plexus	2	5.3	2
Genitofemoral	1	7	3
Ilioinguinal	1	7	7
Intercostal	1	7	7
Lateral femoral cutaneous	3	7	7
Saphenous	1	7	7
Peroneal	2	7	7
Suprascapular	1	4.5	4.5
Sural	1	2.5	2.5
Tibial	5	5.9	6

Pt: Patient.

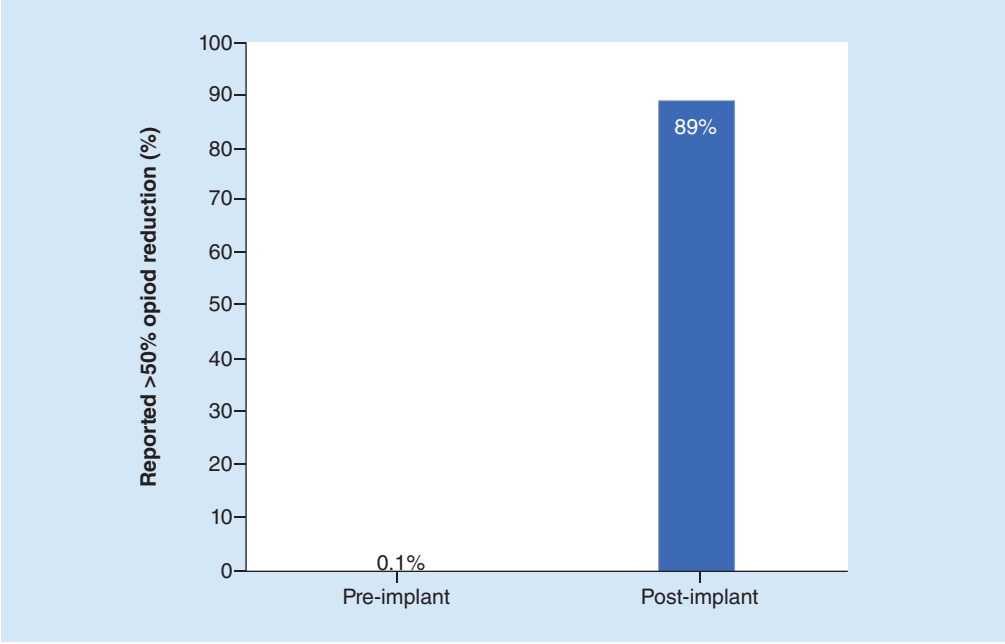

Figure 1. Percent of patients reporting greater than 50% opioid reduction post-implant.

Discussion

Chronic pain currently impacts more than 100 million adults in USA [27–29]. It is estimated that approximately 10% of the US population experiences chronic neuropathic pain [1]. Traditional SCS has been a good treatment option for neuropathic pain but its ability to target specific focal regions is difficult.

The pathophysiology of pain and the mechanism behind neuromodulation is complex. Peripheral nociceptive pain is mediated by the small free nerve endings of Aδ and C fibers. Upon painful stimulation, these small nerves transmit signals to the interneurons of gray matter on the dorsal horn and stimulate second-order neurons to send pain signals to the brain. Upon chronic painful stimulation, nociceptors mediate pain transmission via release of inflammatory neuropeptides (substance P, calcitonin gene-related peptide) at the dorsal horn, stimulating inflammatory cascades that magnify pain responses [30].

Several mechanisms of action for PNS have been proposed, it has been suggested that PNS works via both the Gate Control Theory and via inhibition of neurogenic inflammation [31,32]. The Gate Control Theory was first

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described in 1965 by Malzack and Wall and provides the foundation for current understanding of the therapeutic mechanism behind SCS. Through direct nonpainful orthodromic stimulation by PNS of non-nociceptive Aβ fibers, the dorsal horn interneurons are activated and inhibit the transmission of pain signals from the nociceptive Aδ and C fibers [13,31,33].

It has been postulated that PNS modulates the release of inflammatory neurotransmitters and endorphins directly involved in the pain pathway [31]. Nerve fiber damage during peripheral nerve injury leads to firing and transmission of ectopic discharges through low-threshold Aβ and high-threshold Aδ and C fibers [31]. Studies performed in healthy human volunteers have seen increased pain thresholds in patients undergoing PNS likely attributed to modifications of local inflammatory mediators.

Our case series suggest PNS is effective in controlling pain. Approximately 56% of the participants received upper extremity peripheral nerve stimulators. These regions have historically been considered at higher risk and technically difficult to target with traditional dorsal column SCS. Early PNS symptoms required open surgical implantation and were associated with high levels of iatrogenic nerve [21,22] injury and lead migration [23]. The new PNS system as described previously by Deer *et al.* in his large randomized controlled trial (RCT) study, observed zero device-related severe adverse events and a response rate of 38% [26]. For isolated peripheral mononeuropathies, early evidence suggests peripheral nerve stimulators are less invasive, safer and more effective than traditional SCS. Our results showed that 100% of the patients noted an improvement in their activity and an average VAS reduction score of 71%. Adverse events were not directly evaluated in this study but none were reported to the manufacturer. In contrast, the severe device-related complications for dorsal column SCS or DRG is 18% in refractory neuropathic back and leg pain [34], 11.1% in patients with recurrent radicular pain undergoing SCS after lumbosacral spine surgery [35] and 14% in newer studies on SCS in failed back surgery syndrome [36] compared with 0% severe device-related complications as seen in Deer *et al.* study.

Our data confirm findings seen in Deer *et al.* with overall improvement in self-reported pain scores and increase in functional activity in patients receiving PNS [26]. Notable was a self-reported reduction of opiates by 68%. Additionally, 89% of those implanted with a peripheral nerve stimulator observed a greater than 50% reduction in opioid consumption. As dependence and tolerance to prescription opioid medication continues to rise with increase in morbidity and mortality secondary to opioid use [27,37,38], PNS offers one treatment modality for patients refractory to medical management who continue to suffer from chronic neuropathic pain of peripheral origin.

All (100%) of the questionnaire responders noted improvement in activity with an average of 72% improvement, the greatest being among patients with axillary nerve implantation. The axillary nerve is commonly affected in patients with poststroke shoulder pain. The sensory and motor fibers of the axillary nerve are stimulated as it exits the quadrangular space. The motor portion can be stimulated to reduce subluxation and improve functional activity. Though more randomized controlled trials with PNS are necessary to reaffirm findings seen in our study, the use of PNS may lead to improvement in activity and ultimately quality of life. Studies have shown that chronic pain leads to significant debilitation and depression [39–41]. Thus, PNS may not only help alleviate pain but also provide significant improvement in an individual's overall wellbeing.

With PNS, it is difficult to decide where to place the IPG. If implanting an upper extremity or distal nerve, implantation will have long tunneled leads. The system evaluated in our case series used an IPG secured with adhesive table superficial to the lead's contact points. On average, patients changed their patch every 5 days. From our data, it appears that the more proximal peripheral nerves required more frequent IPG changes while the more distal nerves were changed less frequently. On average, patients used their device 6 out of 7 days of the week. Sustained relief experienced longer than the devices' use is an expected outcome with peripheral neuromodulation.

Our study is limited by its retrospective nature and small sample size making it difficult to draw definitive conclusions. This is a self-reported survey collected by Bioness that is subject to participant response and collection bias. The follow-up time period was limited to 6 months, conclusions on long-term efficacy are unable to be drawn. While we attempted to obtain data from multiple centers, for unclear reasons some locations contributed more to the dataset than others. The data were raw and independently analyzed with no influence by the manufacturer. Adverse events and lead migration was not measured. This is one of the first studies describing the exact nerve location of a PNS implantation and its efficacy. Finch *et al.* published a double-blind crossover trial of 11 PNS patients showing decreased pain response in patients undergoing PNS [25,42]. Our study adds to the literature and supports the conclusions published by Finch *et al.* Further randomized control studies with long-term follow-up are needed to confirm the utility of PNS in alleviating chronic pain.

Early results support the use of PNS as a neuromodulation treatment for mononeuropathy. Our patients experienced improvement in VAS pain scores, reported a decrease in opiate use and improvement in daily function, suggesting that this may be a very viable treatment option for focal mononeuropathy.

Financial & competing interests disclosure

KV Chakravarthy is a consultant to Abbott, Bioness, Medincell, SPR Therapeutics, Nalu Medical, Medtronic, Oska Wellness. He has stock options in Nalu Medical and Oska Wellness. He is the founder of Douleur Therapeutics, NanoAxis and Newrom Biomedical. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that Bioness had obtained patient consents for all survey participants in all of the centers as part of standard of care.

Data sharing statement

The authors certify that this manuscript reports the secondary analysis of clinical trial data that have been shared with them, and that the use of these shared data is in accordance with the terms (if any) agreed upon their receipt. The source of these data are: Bioness Stimulator Survey Data.

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