

PROPHYLACTIC REGENERATIVE PERIPHERAL NERVE INTERFACES IN ELECTIVE LOWER LIMB AMPUTATIONS

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ABSTRACT

Regenerative peripheral nerve interface (RPNI) is a relatively new surgical technique to manage neuromas and phantom pain after limb amputation. This study evaluates prophylactic RPNI efficacy in managing post-amputation pain and neuroma formation in amputees compared with patients in which lower limb amputation was performed without this procedure. We included 28 patients who underwent above the knee amputation (AKA) or below the knee amputation (BKA) for severe soft tissue infection from July 2019 till December 2020. All patients had insulin-dependent diabetes. The patients were divided into two groups, 14 patients with primary RPNI and 14 patients without. We analyzed the demographic data, level of amputation, number of RPNIs, operative time, postoperative complications and functional outcome on the defined follow up period. The mean patient age was 68.6 years (range 49–85), 19 (67.9 %) male and 9 (32.1 %) female patients. In this study 11 (39.3 %) AKA and 17 (60.7 %) BKA were performed. Overall, 37 RPNIs were made. The mean follow-up period was 49 weeks. PROMIS T-score decreased by 15.9 points in favor for the patients with RPNI. The VAS score showed that, in the RPNI group, all 14 patients were without pain compared to the group of patients without RPNI, where the 11 (78.6 %) patients described their pain as severe. Patients with RPNI used prosthesis significantly more ($p < 0.005$). Data showed significant reduction in pain and high patient satisfaction after amputation with RPNIs. This technique is oriented as to prevent neuroma formation with RPNI surgery, performed at the time of amputation. RPNI surgery did not provoke complications or significant lengthening of operative time and it should be furthermore exploited as a surgical technique.

Keywords: RPNI, Phantom Limb Pain, neuroma, amputation, prosthesis

INTRODUCTION

According to the latest statistics (as of 2021), about 10.5% of the adult population suffers from diabetes around the world. [1] Diabetes can cause the development of serious complications of the cardiovascular system, blindness,

renal failure, cerebrovascular complications, peripheral arterial disease, and peripheral limb neuropathies. Persistent peripheral arterial disease, advanced atherosclerosis, and neuropathy in patients with diabetes lead to the development

of chronic wounds of the foot. Chronic wounds in these patients are often accompanied by serious infections that are usually the cause of lower-limb amputations. [2,3,4]

Amputation is challenging to the patients, notwithstanding the phantom limb pain (PLP) which comes along with it. In the literature, as well as in our clinical practice, among patients with lower extremity amputations, phantom limb pain (PLP) occurs often. The reason for the development of PLP is neuroma formation in the amputee stump. Not only this, PLP is yet another reason to limit the patients' daily activity, the use of prosthetic devices, and involvement in daily activities.

In current surgical practice, there are several treatment strategies for neuroma, and Regenerative Peripheral Nerve Interface (RPNI) appears to be one of the methods of neural interfacing for the purpose of bioprosthetic control, mostly due to its organic nature. [5,6]

A review of current literature shows that further research is needed regarding the optimization of RPNI design and its potential use not only for neuroma treatment but also for prophylaxis. Our research in the form of a retrospective case series, surveys the cases of amputation, using the RPNI method at the time of amputation surgery, that were performed at our clinic, up to the date of the writing of this document. In this context, the purposes of this case series were: a) evaluate the technique's efficacy in managing post-amputation pain and neuroma formation in amputees. b) to refine and expand the use of RPNIs for prophylactic purposes.

MATERIAL AND METHODS

The aim of this study is to evaluate the efficacy of prophylactic Regenerative Peripheral Nerve Interfaces (RPNIs) in managing post-amputation pain and neuroma formation in amputees compared with patients where lower limb amputation was performed without this procedure.

The concept of Regenerative Peripheral Nerve Interface (RPNI) is the transfer of a denervated avascular piece of muscle to the surgically discontinued nerve end for the purpose of reinnervation of the transferred muscle tissue and thus showing that it can play the role of a signal

transmitter in the long term. The muscle grafts ($3 \times 1.5 \times 0.5$ cm.) are harvested from expendable skeletal muscle in the residual limb or from a distant site. We used the gastrocnemius muscle as the donor site. Then the muscle grafts are sutured around the distal end of a transected peripheral nerve. This calls for vigilant dissection and identification of the peripheral nerves. The result is an enclosed biologic peripheral nerve interface [5,6]. The grafts are placed so that the fibers of the muscles are in a direction parallel to the axons. In order to allow more signals or to offer the axons more muscle tissue for reinnervation, the individual nerves are split interfascicularly to create several separate nerve endings (Figure 1, 2). The procedure is then repeated accordingly to the number of the transected peripheral nerve endings, which is dependent on the level of amputation. The remainder of the operative procedure is no different than classic amputation procedures.

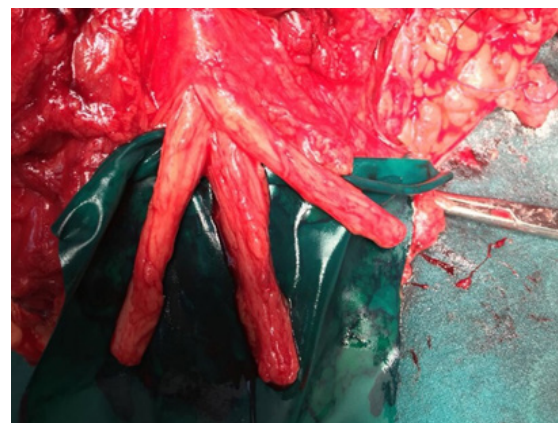


Figure 1. *Transection of primary nerve and intrafascicular split to facilitate reinnervation*



Figure 2. *Suture closure of deinnervated, nonvascularized free muscle graft around distal nerve ending and completed regenerative peripheral nerve interface construction*

This study included 28 patients who underwent above-knee amputation (AKA) or below-knee amputation (BKA) for severe soft tissue infection. All patients had insulin-dependent diabetes. The patients were divided into two groups – 14 patients in which primary RPNI was performed during amputation and 14 patients with amputation without RPNI. We performed an analysis of demographic data, level of amputation, number of RPNI, operative time, postoperative complications as well as the functional outcome on the defined follow up period.

RESULTS

In our study, the mean patient age was 68.6 years (range 49–85), 19 (67.9 %) male and 9 (32.1 %) female patients. Eleven (39.3 %) AKA – above-knee amputations and 17 (60.7 %) BKA – below-knee amputations were performed. Overall, 37 RPNIs were made in the group of patients with primary RPNI (Table 1). Ten out of 14 (71 %) were BKAs with a total number of 26 RPNIs. Eleven RPNIs were done on the tibial nerve, 10 RPNIs on the deep peroneal nerve and 5 RPNIs on the superficial peroneal nerve. Four out of 14 (29 %) were AKAs and 11 RPNIs were performed on the sciatic nerve. In 3 patients, the sciatic nerve was divided into 3 fascicles and in 1 patient in 2 fascicles.

Table 1. Number of RPNIs in every nerve.

Nerve	Number of RPNIs
Sciatic nerve	11
Tibial nerve	11
Deep peroneal nerve	10
Superficial peroneal nerve	5
Total	37

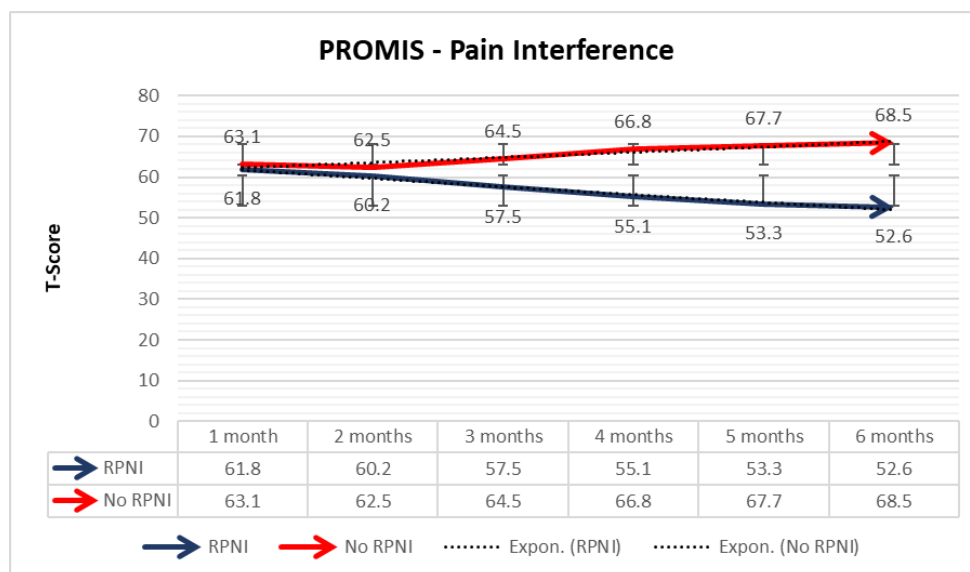
The amputee group without RPNIs was 6 BKAs and 8 AKAs. The mean follow-up period was 49 weeks (range 24–76).

In this study we have used the PROMIS Adult Short Form v1.0 – Pain Interference 8a. The PROMIS Pain Interference score is a standardized score to measure the self-reported consequences of pain on relevant aspects of a patient's life. [7] This

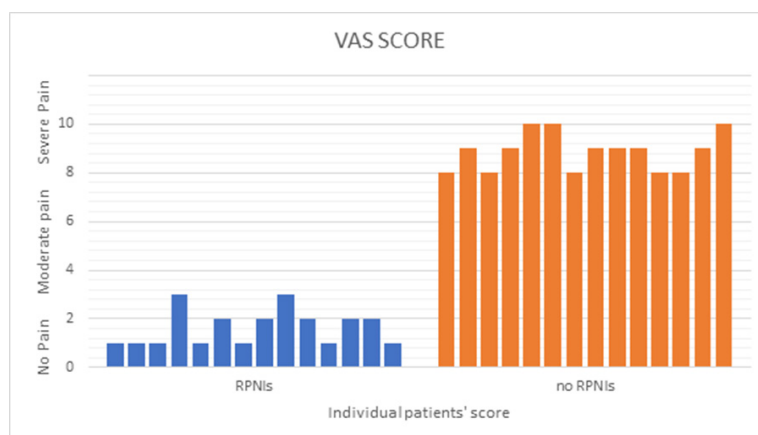
score was based on an average score of 50, formed on responses to the same questions in the general population. Patient-reported outcome measures use answers that patients provide to questions to produce numeric values which indicate patients' state of wellbeing or suffering as well as their ability or lack of ability to function. Therefore, the patients were divided into two groups, as the first one was 14 patients with RPNIs and the second group were 14 amputees without RPNIs. (Figure 3)

In the first group, a 1 month follow up gave us an average T-Score of 61.8, which is higher than in the general population. The 6 Months follow up gave us a decreasing T-score of 52.6, which is closer to the one in the general population. From 1 month follow-up to 6 months follow-up, the pain interference T-score decreased by 9.2 points in the group with RPNIs. The second group was among 14 other patients with amputees and no RPNI. The average T-score in patients with no RPNI in the first month follow up was 63.1 and during the six months follow up was 68.5. There has been an upward tendency and rise in the T-score of 18.5 points higher (worse), compared to the general population. We have compared and evaluated the results at 24 weeks follow up, where the patients with RPNIs had an average T-Score of 52.6 versus a T-score of 68.5 in patients without RPNIs. There is a significant difference between groups at 24 weeks after amputation where the average pain interface T-score is significantly decreased by 15.9 points in favor of the patients with RPNIs.

Six months after amputation the severity of pain was evaluated with VAS (visual analog scale) pain scale. The VAS scale was used to determine the pain intensity in the postoperative phase. [8] Numerical rating from 0 to 10 was used, with 10 being the least comfortable (severe) and 0 being the most comfortable (no pain). In the RPNI group, all 14 patients were without pain compared to the group of patients without RPNI where 11 (78.6%) patients described the pain as severe (Figure 4). Regarding the use of prosthesis, 12 patients with RPNIs started using prosthesis post amputation and had no discomfort. The two remaining patients did not want to regularly use prostheses due to the fitting of the prosthesis. On the other hand, 11 patients without RPNIs did not use prostheses due to pain and discomfort. At our 24 week follow up after the operation, our data showed a significant difference ($p < 0.005$) for the group where RPNI was performed.

Figure 3. Chart of monthly PROMIS–Pain interference during the first 6 months follow-up.

PROMIS – Patient-Reported Outcomes Measurement Information System

Figure 4. VAS score presented in both group of patients. The blue columns show the pain index in patients with RPNi. On the other hand, the orange columns present the second group of amputees without RPNi.

VAS – Visual analog scale

DISCUSSION

The rising trend of circulatory events and metabolic disorders that come with our contemporary lifestyle, contributes greatly to the unfortunate event that is limb loss. [9]

Neuromas represent a severed nerve's attempt at healing. Without a receptive end-organ, nerve endings result in an uncoordinated fashion of axonal sprouting, resulting in swellings of disorganized tissue containing axons, Schwann cells, endoneurial cells, perineurial cells, and fibroblasts in a dense collagenous matrix. The

pathophysiological process starts when the afferent fibers of the severed nerve develop ectopic activity, mechanical sensitivity, and chemosensitivity to catecholamines. On a molecular level, the altered expression of transduction molecules, upregulation of sodium channels, downregulation of potassium channels, and development of nonfunctional connections between axons all lead to hyperexcitability and spontaneous discharge witnessed within injured nerves. On the other hand, PLP is the experience of painful sensations in the missing limb. The science behind it may be ectopic firing from a transected nerve end conjoined with the lack of afferent feedback from the nerve's distal target that may contribute to a symptomatic neuroma. [10, 11, 12]

Known nonsurgical treatments include topical and injectable anesthetics, desensitization, transcutaneous electrical nerve stimulation, topical lidocaine, and adjuvant pain medications such as antidepressants and anticonvulsants. Cases reluctant to the former are treated surgically with simple neuroma excision, nerve capping, and nerve relocation into bone, muscle, or vein. One alternate method is fibrin patch application with the placement of a local pain catheter. [9] Probably because of the nonphysiological nature of these treatments, the long-term outcomes are not nearly ideal. To address this, researchers have been looking for a breakthrough that has the capability to emulate the functions of a native extremity. [10] However, the realization of the full potential of these devices has been hindered by the lack of an optimal interface between the patient and the artificial limb. [13–15]

The quest for ideal interface for nerve regeneration is oriented to the enhancement and stable transmission of nerve signals to provide fine motor control, promote integration with surrounding tissues, and avoid iatrogenic axonal damage within the peripheral nerve. To go a step further, it is highly recommended to have the potential to prevent and treat neuropathic pain related to symptomatic neuromas. [16–18]

While functional prosthetics are an admirable goal, the main goal of peripheral nerve management at the time of amputation should be to limit, improve, or eliminate the potential for neuropathic pain and PLP. [19] The incidental breakthrough with RPNI has changed the landscape of management and improved the overall quality of life of these patients. Initially designed to harness voluntary motor nerve signals for neuroprosthetic control, plastic surgeons coincidentally came to the discovery that RPNI is a decent strategy for neuroma pain management in amputees. RPNIs are neuromuscular surgical constructions that serve as a biological interface. Neurotization of the muscle grafts by the terminal branches of the residual nerves is followed by revascularization, regeneration, and eventually reinnervation. These phases allow the RPNI to mature in 3 to 4 months and transduce evoked muscle potentials for up to 18 months. The simple biological design not only acts as a conduit but acts as a protective cushion that prevents iatrogenic damage by manipulation. [20–24]

This technique has accomplished to provide a physiologic end-organ to allow the neuronal regenerative signals to close their feedback circuit and suppress ectopic impulses that lead to neuropathic pain. [25–28] Moreover, it provides sensory feedback to the sensorimotor cortex. Simply put, “it gives the nerve somewhere to go, and something to do” by attaching neuromuscular endplates in the denervated muscles that are functionally made “empty” and, thus more welcoming to neurotization from the regenerating peripheral nerve. [29, 30] The “regenerative” nature of RPNIs can be attributed to the relation between the free muscle grafts and the nerves in question. The muscle grafts initially go over degeneration followed by regeneration and accompanied by reinnervation that occurs through a well-described series of neurotrophin – mediated events. The end products are viable neuromuscular junctions, that, according to previous studies, mature in 3 to 4 months and transduce evoked muscle potentials for up to 18 months. Dissimilar to the many existing methods to surgically treat neuromas, RPNIs have gained “fame” thanks to their physiological essence, and the procedure’s uprising practice is sensible. Taking advantage of the body’s own features, this technology is found to be convenient by more and more surgeons around the globe. [31–34]

CONCLUSION

Prophylactic Regenerative Peripheral Nerve Interfaces in major limb amputees resulted in a lower incidence of both symptomatic neuromas and phantom limb pain compared with control patients undergoing amputation without Regenerative Peripheral Nerve Interfaces, suggesting that prevention of peripheral neuromas following amputation may diminish the central pain mechanisms that lead to phantom limb pain. Raising important questions concerning optimization of RPNI’s design purposes.

Future studies focused on the amputee patient population are needed to explore the potential indications for RPNI surgery.

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Резиме**ПРОФИЛАКТИЧЕН РЕГЕНЕРАТИВЕН ПЕРИФЕРЕН НЕРВЕН ИНТЕРФЕЈС
КАЈ ЕЛЕКТИВНИ АМПУТАЦИИ НА ДОЛЕН ЕКСТРЕМИТЕТ**

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Регенеративниот периферен нервен интерфејс (РПНИ) е релативно нова хируршка метода, која се користи за превенција во појавата на невриноми, како и на фантомска болка по ампутација на екстремитет. Целта на оваа студија е да ја процени ефикасноста на превентивната РПНИ-процедура кај пациентите со апмутиран екстремитет, споредено со пациентите на кои не им е направена оваа хируршка техника. Вклучивме 28 пациенти кои имале натколенична или потколенична ампутација поради тешка мекоткивна инфекција во периодот од јули 2019 година до декември 2020 година. Сите пациенти имаат инсулин зависен дијабетес мелитус. Пациентите се поделени во две групи од по 14 пациенти со примарен РПНИ и 14 пациенти без РПНИ. Се анализираа демографските статистики, нивото на ампутација, бројот на РПНИ, оперативното време, постоперативните компликации и функционалноста во одреден контролен период. Средната возраст на пациентите е 68,6 години (ранг 49–85), од кои 19 (67,9 %) се мажи и 9 (32,1 %) жени. Во оваа студија беа направени 11 (39,3 %) натколенични ампутации и 17 (60,7 %) потколенични ампутации. Беа направени 37 РПНИ. Просечниот период на следење беше 49 недели. ПРОМИС Т-вредноста е намалена за 15,9 поени во корист на пациентите со РПНИ. ВАС-скорот покажа дека во групата со РПНИ сите 14 пациенти се без болка, во споредба со групата пациенти без РПНИ, каде што 11 пациенти (78,6 %) ја опишале болката како неиздржлива. Групата со РПНИ покажа значајна разлика при употребата на протеза ($p < 0,005$). Податоците покажаа значително намалување на болката и задоволство на пациентите по ампутацијата со РПНИ. Оваа техника има цел да го спречи формирањето невром. Техниката на РПНИ не предизвика компликации или значително продолжување на оперативното време и треба да се искористи како хируршка техника.

Клучни зборови: РПНИ, фантомска болка, неуром, ампутација, протеза