

ACTIVE NERVE MANAGEMENT IN AMPUTATION: RPNI AS A STRATEGY TO ELIMINATE NEUROMA FORMATION AND TRANSFORM POSTAMPUTATION OUTCOMES

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ABSTRACT

Background: Symptomatic neuroma formation and chronic post-amputation pain remain major barriers to functional recovery following lower limb amputation. Active nerve management strategies, such as the Regenerative Peripheral Nerve Interface (RPNI), have emerged as promising techniques for preventing neuropathic pain by providing a biological target for transected nerves.

Methods: A retrospective observational study was conducted including 24 adult patients who underwent transfemoral or transtibial amputation. Twelve patients received prophylactic RPNI at the time of amputation, while 12 underwent standard amputation without active nerve management. Incidence of symptomatic neuroma, Tinel's sign, pain intensity (VAS), pain interference (PROMIS Pain Interference 8a) and prosthetic use were evaluated over a 12-week follow-up period.

Results: No cases of symptomatic neuroma were observed in the RPNI group (0%), compared to 66.7% in the control group ($p < 0.001$). At 12 weeks, mean VAS pain scores were significantly lower in the RPNI group (0.4 ± 0.8) compared to controls (5.8 ± 1.7 ; $p < 0.0001$). PROMIS Pain Interference scores at 3 months were markedly improved in the RPNI group (44.0 ± 4.5) versus the control group (66.0 ± 5.8 ; $p < 0.001$). A higher proportion of RPNI patients successfully used a prosthesis (66.7% vs. 41.7%), although this difference did not reach statistical significance.

Conclusion: Prophylactic RPNI during lower limb amputation effectively prevents symptomatic neuroma formation and significantly reduces post-amputation pain, with favorable functional outcomes. These findings support routine active nerve management as a strategy to optimize rehabilitation and quality of life in amputee patients.

Keywords: RPNI, pain, neuroma, VAS, PROMIS

INTRODUCTION

According to the global epidemiological data, more than one million limb amputations are performed annually worldwide [1]. One of the most common and clinically significant consequences of amputation is post-amputation pain, encompassing both phantom limb pain and residual limb pain, which represents a major factor

impairing the functional recovery and the overall quality of life [2]. The key pathophysiological mechanism underlying this symptomatology is the development of a symptomatic neuroma at the distal end of the transected nerve. A neuroma represents a disorganized regenerative response characterized by aberrant axonal sprouting within

a fibrotic microenvironment. It is estimated to occur in 10–25% of amputees and frequently serves as the primary source of persistent residual limb pain [3]. Phantom limb pain often coexists with neuroma-related pain, further complicating rehabilitation and prosthetic acceptance [2]. Although substantial scientific attention has been directed toward phantom limb pain, considerably fewer studies have focused on the prevention and surgical management of symptomatic neuromas [4].

Currently, no universal gold standard has been established for the prevention of post-amputation pain [4]. Traditional surgical approaches including neurectomy, nerve transposition into various anatomical structures and specialized nerve-end closure techniques have demonstrated variable and often unpredictable outcomes [5]. These methods are predominantly passive in nature and fail to provide an adequate biological environment for directed axonal regeneration, thereby contributing to recurrent neuroma formation and chronic pain development [6].

In response to this clinical challenge, the past two decades have witnessed the development of active reconstructive techniques that offer a biological “target” for axonal growth. Among the most prominent are Targeted Muscle Reinnervation (TMR) and Regenerative Peripheral Nerve Interface (RPNI). Initially designed to improve myoelectric prosthetic control, TMR involves coapting transected sensory nerves to motor branches of residual muscles and has demonstrated a significant reduction in the incidence of symptomatic neuroma formation and phantom limb pain [7].

RPNI represents a biologically simplified technique in which the transected nerve is implanted into a small autologous denervated muscle graft, allowing for integrated and organized neuromuscular regeneration [8]. Originally developed by Cederna and colleagues and first applied in upper extremity amputations, subsequent studies have demonstrated that prophylactic application of RPNI in lower limb amputations significantly reduces symptomatic neuroma formation, pain intensity, and the need for revision surgery [10–12].

The contemporary paradigm in amputation surgery is shifting from treatment of established complications toward prevention at the time of the primary procedure. Within this evolving framework, RPNI emerges as a promising technique with the potential to become a new standard approach for the prevention of chronic post-amputation pain

and symptomatic neuroma formation in patients undergoing lower limb amputation [11, 12].

MATERIALS AND METHODS

This study was designed as a retrospective observational clinical investigation conducted at the University Clinic for Plastic and Reconstructive Surgery. A total of 24 patients were included in the present analysis and were divided into two equal groups of 12 patients each. The study group consisted of patients who underwent limb amputation with prophylactic application of the Regenerative Peripheral Nerve Interface (RPNI) technique, whereas the control group included patients who underwent standard amputation without RPNI as part of the surgical protocol.

Eligible participants were adults older than 18 years who underwent either transfemoral (above-knee) or transtibial (below-knee) amputation. Patients younger than 18 years of age, those undergoing amputations limited to toes or partial foot resections, as well as patients treated with guillotine or extra-anatomical amputations, were excluded from the analysis.

RPNI constructs were formed intraoperatively. Following the standard identification and transection of the peripheral nerve, the terminal nerve end was carefully prepared and implanted into an autologous denervated muscle graft measuring approximately $3 \times 1.5 \times 1$ cm. The muscle graft was harvested from viable muscle tissue of the amputated limb or the residual stump, depending on the level of amputation (e.g., vastus lateralis in transfemoral amputations and gastrocnemius in transtibial amputations). The nerve end was secured within the muscle graft using two epineural sutures with 7-0 non-absorbable monofilament. The muscle graft was then wrapped around the nerve and stabilized using epimysial sutures to ensure adequate containment and structural support. In cases involving larger nerves, such as the sciatic nerve, intraneural dissection was performed to separate individual fascicles, allowing the creation of multiple RPNI constructs per fascicular unit. The average operative time required to construct each RPNI unit was approximately 7–10 minutes. The remaining steps of the amputation procedure were performed according to the standard surgical principles, with particular

attention to graft positioning in order to prevent superficial compression.

Postoperative follow-up evaluations were conducted at 1, 4, 8, and 12 weeks after surgery. Pain intensity was assessed using the Visual Analog Scale (VAS, 0–10) at each follow-up visit. The impact of pain on daily functioning was evaluated at weeks 4, 8, and 12 using the PROMIS Pain Interference 8a questionnaire. The presence of a positive Tinel's sign was assessed at weeks 4, 8, and 12. At 12 weeks postoperatively, the use of a prosthetic device was documented. The clinical diagnosis of symptomatic neuroma was established based on the presence of a positive Tinel's sign in conjunction with characteristic clinical findings, including localized hypersensitivity and paresthesia.

RESULTS

A total of 24 patients were included in the study, with 12 patients allocated to the RPNI group and 12 to the control group. The mean age in the RPNI group was 67.8 ± 8.96 years, compared to 61.1 ± 12.0 years in the control group. The difference in age distribution between the groups was not statistically significant ($p = 0.15$).

Sex distribution varied between the two cohorts. The RPNI group predominantly con-

sisted of male patients (10 males and 2 females), whereas the control group included a higher proportion of female patients (4 males and 8 females). Although this difference approached statistical significance, it did not reach the conventional threshold (Fisher's exact test, $p = 0.065$). This imbalance is considered a consequence of case selection and should be taken into account when interpreting the results.

Regarding the etiology of amputation, vascular causes predominated in both groups, most commonly peripheral arterial disease and diabetic gangrene. In the RPNI group, diabetic gangrene was the leading indication, present in 9 out of 12 patients (75%). The remaining three cases included one patient with osteomyelitis (8.3%), one with vascular disease without a diabetic component (8.3%), and one with malignancy as the primary indication for amputation (8.3%). In the control group, 7 of 12 patients (58.3%) underwent amputation due to diabetic gangrene, while the remaining 5 patients (41.7%) had vascular disease as the primary indication. No cases of osteomyelitis or malignancy were recorded in the control cohort (Figure 1).

With respect to the level of amputation, an equal distribution of transfemoral and trans-tibial amputations was observed in both groups. In each cohort, 8 patients (66.7%) underwent above-knee amputation and 4 patients (33.3%)

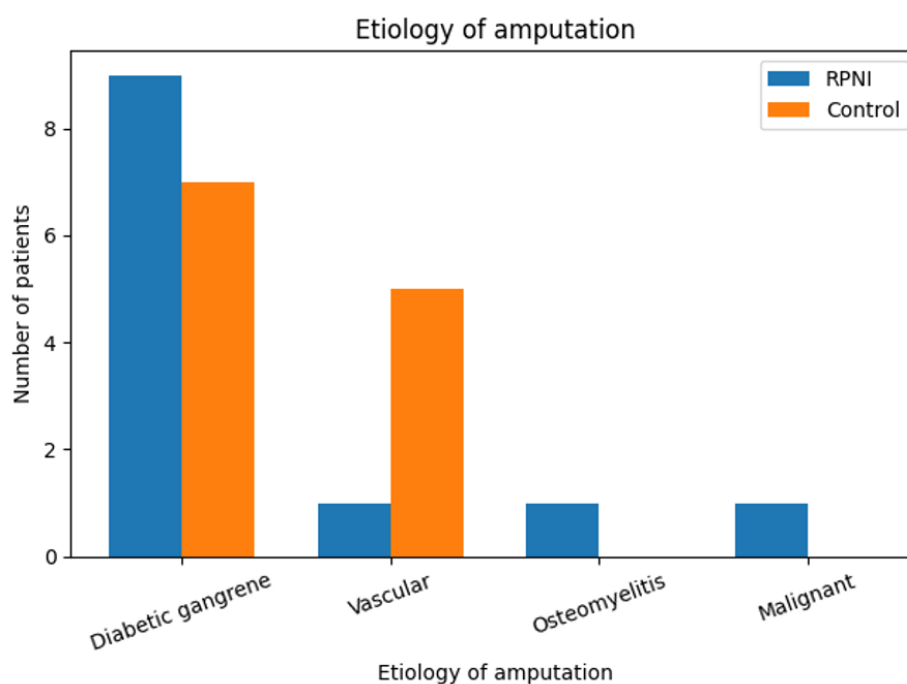


Figure 1. Distribution of patients according to the etiology of amputation

underwent below-knee amputation. The groups were therefore homogeneous in terms of amputation level ($p = 1.00$).

In the RPNI group, a mean of 2.3 ± 1.0 RPNI constructs were performed per patient, corresponding to implantation of two to three major peripheral nerves into muscle grafts, depending on the level of amputation.

Incidence of Symptomatic Neuroma and Tinel's Sign

Tinel's sign was used as an early clinical indicator of nerve regeneration and potential symptomatic neuroma formation. At the first postoperative evaluation, 4 weeks after amputation, 11 of 12 patients (91.7%) in the control group demonstrated a positive Tinel's sign upon percussion of the residual limb. In contrast, none of the patients in the RPNI group exhibited a positive Tinel's sign at 4 weeks. Percussion over the sites where nerves had been implanted into muscle grafts did not elicit sharp dysesthesia or localized pain.

At 8 weeks postoperatively, 8 patients in the control group continued to demonstrate a positive Tinel's sign, whereas the RPNI group remained negative for Tinel's sign. At 12 weeks, the same 8 patients in the control group maintained a positive Tinel response, with no cases observed in the RPNI cohort.

All patients were clinically evaluated for the development of symptomatic neuroma during follow-up. A statistically significant difference was observed between the two groups. In the RPNI group, none of the 12 patients (0%) developed symptomatic neuroma at any follow-up time point (4, 8, or 12 weeks post-amputation). In contrast, 8 of 12 patients (66.7%) in the control group developed clinically symptomatic neuromas, defined as a localized, highly tender point within the residual limb associated with a positive Tinel's sign. These patients reported pain upon palpation and during prosthetic use.

The difference in symptomatic neuroma incidence between the two groups was highly statistically significant (Fisher's exact test, $p < 0.001$). In other words, prophylactic RPNI in this series completely prevented the development of clinically manifest neuromas, whereas two-thirds of the patients undergoing standard amputation developed this complication.

Visual Analog Scale (VAS) Pain Scores

Subjective pain intensity in the residual limb and phantom limb was quantified using the Visual Analog Scale (VAS, 0–10). At the end of the first postoperative week, all patients reported some degree of pain, and no statistically significant difference was observed between the groups at that time point.

However, differences became evident during the subsequent follow-up. At 4 weeks post-amputation, patients in the control group reported severe pain, with a mean VAS score of 7.2 ± 1.5 . In contrast, patients in the RPNI group demonstrated significantly lower pain levels, with a mean VAS score of 3.7 ± 2.0 , corresponding to moderate pain intensity. This difference was highly statistically significant (independent samples t-test, $p < 0.001$).

At 8 weeks, the mean VAS scores decreased to 1.8 ± 1.3 in the RPNI group, whereas the control group demonstrated a mean score of 5.0 ± 2.0 . By 12 weeks postoperatively, the RPNI group showed near-complete resolution of pain, with a mean VAS score of 0.4 ± 0.8 . Although the pain levels in the control group decreased compared to earlier time points, they remained within the moderate-to-severe range, with a mean VAS score of 5.8 ± 1.7 (Figure 2).

The difference in pain intensity at 12 weeks was extremely statistically significant ($p < 0.0001$).

PROMIS Pain Interference – Impact of Pain on Function

Beyond pain intensity, the functional impact of pain on daily life was evaluated using the PROMIS Pain Interference 8a questionnaire, which generates standardized T-scores (population mean = 50). Higher T-scores indicate greater pain-related interference with physical and social activities, whereas lower scores reflect less functional impairment. Scores below 50 represent levels of interference lower than the average general population.

At 4 weeks post-amputation, the control group demonstrated markedly elevated Pain Interference scores, with a mean T-score of approximately 65, indicating substantial disruption of mobility, standing tolerance, sleep, and social participation due to pain. In contrast, patients in the RPNI group showed significantly lower PROMIS T-scores at the same time point

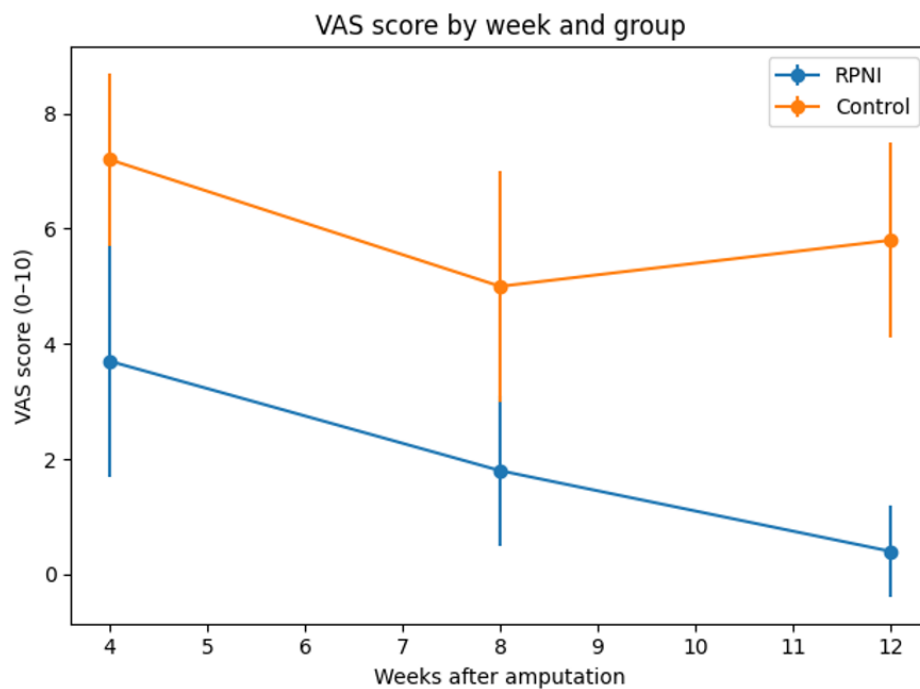


Figure 2. VAS score for the study and control groups

(approximately $T = 55$), corresponding to mild to moderate pain-related interference. The between-group difference of approximately 10 T-score points was statistically significant ($p = 0.004$).

The divergence between the groups became even more pronounced at subsequent follow-up evaluations. At 12 weeks postoperatively, the mean PROMIS T-score in the RPNI group was 44.0 ± 4.5 , falling below the normative population average and indicating minimal functional limitation attributable to pain. Conversely, the control group demonstrated a mean T-score of 66.0 ± 5.8 at 12 weeks, reflecting severe and persistent interference of pain across multiple domains of daily life (Table 1).

The between-group difference of approximately 22 T-score points at 3 months was highly statistically significant ($p < 0.001$).

Prosthetic Use and Rehabilitation

One of the key outcomes following major limb amputation is the patient's ability to successfully adapt to and regularly use a prosthetic device, thereby facilitating reintegration into daily life and restoration of functional independence. For this reason, prosthetic utilization was assessed at 12 weeks postoperatively.

In the RPNI group, 8 of 12 patients (66.7%) reported regular prosthetic use, while 4 patients (33.3%) had not successfully adapted to or were not using a prosthesis at the time of evaluation. In contrast, only 5 of 12 patients (41.7%) in the control group were actively using a prosthesis, whereas 7 patients (58.3%) were not rehabilitated to the level of prosthetic use.

Although the difference between groups did not reach statistical significance ($p = 0.14$), the observed trend suggests a clinically meaning-

Table 1. Mean PROMIS Pain Interference T-scores at 12 weeks after amputation

Group	PROMIS PI T-score (mean $\pm$ SD) at 12 weeks	95% Confidence Interval
RPNI (n = 12)	44.0 ± 4.5	41.5 – 46.5
Control (n = 12)	66.0 ± 5.8	62.5 – 69.5
Difference	22.0 points (higher in the control group)	$p < 0.001$

Note: Higher T-score indicates greater pain interference. The difference between the groups was tested using an independent t-test.

ful advantage in functional rehabilitation among patients who underwent prophylactic RPNI at the time of amputation.

DISCUSSION

Our study clearly demonstrates the benefit of prophylactic RPNI in preventing symptomatic neuroma formation following lower limb amputation. In the RPNI cohort, no cases of clinically symptomatic neuroma were observed, compared to a 66.7% incidence in the control group. This represents a dramatic and statistically significant reduction, indicating that implantation of the transected nerve into a denervated muscle graft effectively prevents the disorganized axonal regeneration that leads to neuroma formation.

These findings are consistent with the growing body of evidence suggesting that active nerve management techniques can prevent neuroma formation and chronic residual limb pain [5,8]. A recent retrospective study confirmed that RPNI significantly reduces neuroma formation and associated pain in lower extremity amputations [8]. Similarly, Kubiak et al. reported that prophylactic implantation of transected nerves into muscle (RPNI) is associated with a marked reduction in post-amputation complications [5].

Beyond neuroma prevention, our data demonstrate a substantial impact of RPNI on post-amputation pain. Although early postoperative pain levels were comparable between groups, significant differences emerged during follow-up. At 4 weeks, the mean VAS score in the RPNI group was approximately 3.7 (moderate pain), compared to 7.2 (severe pain) in controls. By 12 weeks, pain in the RPNI group had nearly resolved (mean VAS 0.4), whereas the control group continued to experience moderate-to-severe pain (mean VAS ~5.8).

This profound reduction in both residual and phantom limb pain aligns with previous studies employing active reinnervation strategies. Woo et al. reported a 71% reduction in neuroma pain and a 53% reduction in phantom pain following RPNI in patients with chronic post-amputation neuroma pain [7]. Our findings mirror these improvements and further suggest that addressing nerve endings at the time of amputation may significantly mitigate both residual limb and phantom limb pain.

Importantly, similar outcomes have been demonstrated with Targeted Muscle Reinnervation (TMR), which also provides a physiologic target for transected nerves. In a randomized controlled trial, Dumanian et al. showed that patients undergoing major limb amputation with TMR experienced significantly lower phantom and residual limb pain compared to standard surgical management [29]. Furthermore, systematic reviews indicate that performing TMR or RPNI at the time of amputation results in superior pain control, reduced disability, and a lower incidence of symptomatic neuromas compared to conventional approaches [28]. Retrospective comparative analyses have suggested that both TMR and RPNI achieve similarly effective neuroma prevention and pain relief, without significant differences between techniques [30].

Collectively, these data reinforce the concept that active peripheral nerve redirection techniques, whether RPNI or TMR, are substantially more effective in controlling post-amputation neuropathic pain than traditional passive strategies. Conventional methods do not actively guide axonal regeneration, allowing transected nerves to form disorganized neuromas or regenerate into fibrotic scar tissue [17,20].

In contrast, RPNI directs regenerating axons into a small denervated muscle graft, where organized reinnervation of muscle fibers occurs instead of neuroma formation [15]. The muscle graft serves as a biological target and functional “end-organ”, thereby eliminating the pathophysiologic substrate for symptomatic neuroma development. The conceptual foundation for this approach was initially proposed by Dellon and Mackinnon, who demonstrated that implantation of a transected nerve into muscle could reduce neuroma pain [12]. The modern RPNI technique refines this principle through the use of small free muscle grafts harvested from the amputated limb, secured with microsurgical precision to optimize reinnervation and minimize recurrent neuroma formation [7,12].

Preclinical evidence further supports this mechanism. Experimental animal models have demonstrated that implantation of the sciatic nerve into a denervated muscle graft completely prevents neuroma formation and the development of neuropathic pain behaviors, thereby confirming the biological validity of this approach [25].

Restoration of mobility and functional independence remains one of the ultimate goals following major limb amputation. Chronic residual limb pain and neuroma-related hypersensitivity can significantly hinder prosthetic tolerance and rehabilitation progress [2]. In our study, a higher proportion of patients in the RPNI group were successfully using a prosthesis at 3 months (66.7%) compared to controls (41.7%). Although this difference did not reach statistical significance due to sample size limitations, the observed trend suggests that the substantial pain reduction achieved with RPNI may facilitate improved prosthetic adaptation and rehabilitation outcomes. Previous studies have similarly reported that reduction of neuroma-related pain correlates with improved prosthetic wear and mobility [2,15].

Despite these promising findings, several limitations should be acknowledged. The sample size was relatively small ($n = 24$), limiting the statistical power and precluding detailed subgroup analyses. The follow-up period was restricted to 12 weeks; although no neuromas were observed in the RPNI group during this interval, longer-term evaluation is necessary to confirm the durability of these outcomes. Furthermore, the group allocation was not randomized, but it was based on clinical practice patterns, introducing potential selection bias.

Nevertheless, despite these limitations, the magnitude and consistency of the observed differences are compelling and align with the global trends in contemporary amputation surgery.

An increasing body of evidence supports the integration of active nerve reconstructive techniques at the time of primary amputation to improve patient outcomes [5,28,29]. Our findings contribute to this evolving paradigm shift – from reactive treatment of chronic post-amputation pain toward its prevention during the initial surgical procedure.

Given the dramatic reduction in symptomatic neuroma formation, significant attenuation of post-amputation pain, and improved functional trends observed in our cohort, prophylactic RPNI demonstrates strong potential to become a standard component of modern amputation surgery, particularly in lower limb amputations.

Future large-scale, prospective, and randomized studies with extended follow-up are warranted to definitively establish the long-term benefits of RPNI and to further define its

role as a routine surgical strategy aimed at optimizing functional recovery and quality of life in amputee patients.

CONCLUSION

Prevention of post-amputation neuroma formation and chronic neuropathic pain is essential for successful rehabilitation following major limb amputation. Our study demonstrates that prophylactic application of the Regenerative Peripheral Nerve Interface (RPNI) during lower limb amputation effectively eliminates symptomatic neuroma formation and significantly reduces both phantom and residual limb pain.

Patients treated with RPNI experienced minimal to no chronic pain, improved functional outcomes, and a higher likelihood of successful prosthetic use compared with patients undergoing standard amputation without active nerve management. These findings are consistent with the growing body of evidence supporting targeted nerve management strategies as highly effective interventions for preventing symptomatic neuromas and mitigating post-amputation pain.

Given its favorable clinical impact, RPNI may be recommended as a routine component of surgical technique in major lower limb amputations, particularly in patients with anticipated long-term survival and active prosthetic use. The benefits of this approach extend beyond pain control, facilitating accelerated rehabilitation, enhanced mobility, and improved quality of life.

Our findings contribute to the emerging consensus that every transected nerve at the time of amputation should be actively managed in order to prevent symptomatic neuroma formation and optimize long-term functional outcomes.

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Резиме**АКТИВЕН НЕРВЕН МЕНАЏМЕНТ КАЈ АМПУТАЦИЈАТА:
РПНИ КАКО СТРАТЕГИЈА ЗА ЕЛИМИНИРАЊЕ НА ФОРМИРАЊЕТО
НЕВРОМИ И ТРАНСФОРМИРАЊЕ НА ИСХОДИТЕ ОД ПОСТАМПУТАЦИЈАТА**

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Вовед: Формирањето на симптоматски невроми и хроничната постампутициска болка претставуваат значајни пречки за функционалното закрепнување по ампутиација на долните екстремитети. Активните техники за згрижување на нервите, како што е регенеративниот периферен нервен интерфејс (РПНИ), се релативно нови техники, кои се користат за превенција на невропатската болка преку обезбедување таргет-структура за пресечените нерви.

Методи: Се направи ретроспективна опсервациска студија, која вклучува 24 пациенти кај кои е направена потколенична или натколенична ампутиација. Кај 12 пациенти е применет профилактички РПНИ во текот на ампутиацијата, додека кај 12 е изведена стандардна ампутиација. Инциденцата на симптоматски невром, присуството на Тинеловиот знак, интензитетот на болката (VAS), влијанието на болката (PROMIS Pain Interference 8a) и користењето на протеза беа евалуирани во период на следење од 12 недели.

Резултати: Во групата РПНИ не беа забележани случаи на симптоматски невром (0 %), во споредба со 66,7 % во контролната група ($p < 0,001$). По 12 недели, просечните VAS-вредности за болка беа значајно пониски во групата РПНИ ($0,4 \pm 0,8$) во споредба со контролите ($5,8 \pm 1,7$; $p < 0,0001$). PROMIS Pain Interference резултатите по три месеци беа значително подобри во групата РПНИ ($44 \pm 4,5$) во однос на контролната група ($66 \pm 5,8$; $p < 0,001$). Поголем процент пациенти во групата РПНИ успешно користат протеза (66,7 % наспроти 41,7 %), иако оваа разлика не достигна статистичка значајност.

Заклучок: Употребата на профилактички РПНИ при ампутиација на долен екстремитет е ефикасен во превенцијата на формирањето симптоматски невроми и значајно ја намалува постампутициската болка, со поволни функционални исходи. Овие резултати ја поддржуваат рутинската примена на активен нервен менаџмент како стратегија за оптимизација на рехабилитацијата и на квалитетот на живот кај пациентите со ампутиации.

Клучни зборови: РПНИ, болка, невром, VAS, PROMIS