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Review article

NO PAIN IS A PATIENT'S GAIN – A REVIEW OF SURGICAL TECHNIQUES FOR PREVENTION AND TREATMENT OF POSTAMPUTATION PAIN

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Abstract

Regardless of the cause, major lower limb amputation is a life-changing event and accompanied by pain it has a great impact on patients' quality of life. Over the years many pharmacological and surgical treatments have been tried to manage residual limb pain and phantom limb pain, but they were either unsuccessful or did not apply to all patients. The aim of this review paper was to describe the current modalities of treatment of postamputation pain and the opportunity to use surgical techniques as prophylactic. More than 150 surgical interventions have been described in the literature: traction neurectomy, nerve capping, end-to-end nerve coaptation, nerve transposition, etc. New and efficient techniques are regenerative peripheral nerve interface and targeted muscle reinnervation initially described for bioprosthetic control. Results from recent studies have shown that these techniques can be used for treatment, but also in a prophylactic manner, which can only be of benefit for the patient.

Keywords: phantom limb pain, residual limb pain, neuroma, amputation, RPNI

Introduction

There are many reasons for major limb amputation, starting with traumatic amputations due to traffic accidents or war-related, affecting usually young people. One part of amputations are due to tumor resection, but the most common cause especially for lower limb amputations are peripheral vascular diseases and diabetes. All patients experience some kind of pain immediately or a few weeks after the surgery[1]. The amputation itself is a life-changing event and accompanied by pain it has a great impact on patients' well-being and social life.

Over the years many pharmacological and surgical treatments have been tried to manage the postamputation pain, but they were either unsuccessful or did not apply to all patients. Little was known about the mechanisms of pain and surgically speaking, it was advised to avoid handling the nerve. Even though today a great progress is made not only in treatment of postamputation pain, but also in prevention, there is still no gold standard[2].

Phantom limb pain (PLP), residual limb pain (RLP) and phantom limb sensation (PLS) are often overlapping and coexist in the same patient; it is difficult to distinguish them, but they need to be addressed to[1]. The aim of this review was to describe the current modalities of treatment of postamputation pain and to use surgical techniques to prevent PLP and RLP.

More than 2000 papers have been published about phantom limb pain and treatment, but only a small number of articles describe surgical techniques for treatment of symptomatic end-neuromas.

Definition of phantom limb pain and residual limb pain

Phantom phenomenon as a term has been known since ancient times. It includes two entities: phantom limb pain and phantom limb sensation. Patients usually report a feeling that the missing part of the extremity is still present[3-5]. Non-painful manifestations are called phantom limb sensations (PLS) and they do not require treatment. In contrast, pain in the missing limb is called phantom limb pain (PLP), which causes discomfort and diminishes the quality of life. Stump pain or residual limb pain (RLP) is common immediately after surgery and even though usually subsides within a few weeks, it can develop as a chronic stump pain [4-6].

Despite the complex mechanism of PLP as a result of morphological, chemical and physiological changes in both peripheral and central nervous system, understanding the molecular physiology of neuroplastic changes and central sensitization is an asset in pain management and treatment, especially for targeted pharmacological therapy[3,7, 11-12]. The origin of PLP and RLP from the peripheral nerve system is neuropathic pain due to end-neuroma formation[14]. After complete nerve transection not followed by nerve repair as in limb amputation, the axons from the proximal end attempt to sprout and regenerate, but because there is no distal target, the nerve forms disorganized bulky mass at its end[8-10]. Patients usually describe RLP as sharp, stabbing, burning. The diagnosis of symptomatic end-neuroma can be done clinically using the Tinel's sign elicited by percussion on the site[9]. Although not necessarily, but imaging technologies (ultrasonography and MRI) can also be used for better neuroma localization.

Conservative treatment

The conservative strategies for treatment of PLP and RLP include pharmacotherapy using tricyclic antidepressants, gabapentin, opioids and NMDA receptor antagonists. Other used modalities are physical therapy, mirror therapy and other less invasive techniques as desensitization, transcutaneous electrical stimulation or local injection of anesthetics[3, 13, 22]. Nevertheless, none of the proposed solutions have major effect and patients continue to report either pain in the missing extremity or pain in the residual part.

Surgical treatment – resect the bulb!

Recent studies have shown that even though there is no consensus on the proper surgical technique for treating PLP and RLP, surgery can alleviate postamputation pain and improve quality of life. Different surgical interventions have been described in the literature, but no matter the technique used, always resect the neuroma![14] (Figure 1). The simplest way is to retract the nerve and transect proximally (traction neurectomy) so that the nerve will retract between muscles in the stump, far from the skin; even if a neuroma occurs, it would not be painful[15,16]. The limitation of this treatment is that one does not have control of the nerve end and pain can appear, hence, the patient will be limited in wearing prosthesis or sitting in a wheelchair[17].

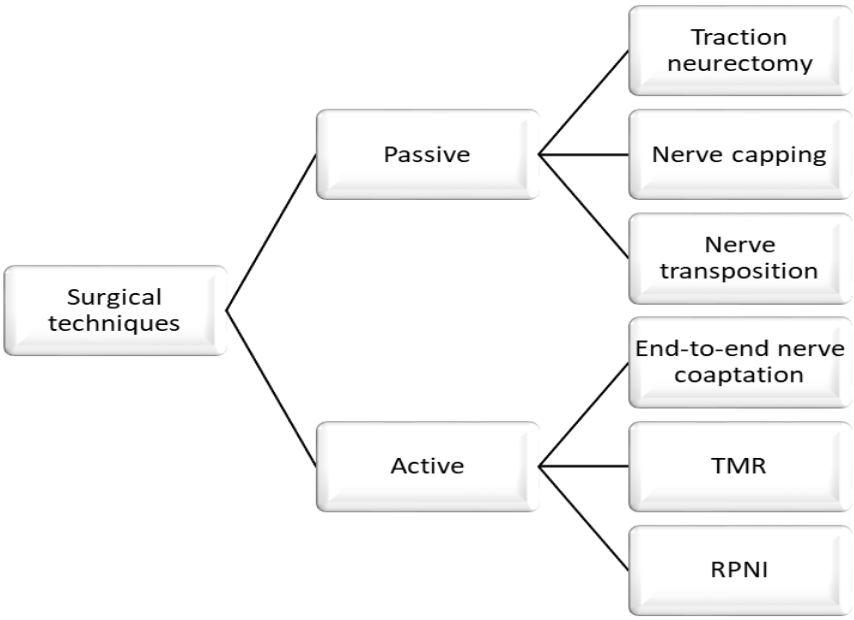

Fig. 1. Active and passive surgical techniques for neuroma treatment

Prevention of pain

Most of the current surgical techniques are effective in prevention of the postamputation pain and neuroma formation if the procedure is carried out during primary intervention (during amputation)[18]. Nevertheless, they are underutilized especially if the amputation is not done by a plastic surgeon and nerves get disregarded. Prophylactic surgical strategies should be considered nowadays when modern and functional prosthetics are available and amputation is not a prison sentence.

Nerve transposition

Regardless of the fact when the basic surgical method is applied, whether following neuroma excision or prophylactic nerve handling, it consists of implanting the end of the residual nerve into a local innervated muscle, which was reported for the first time in 1918[19]. In 1984 and 1985, Dellon and Makkinnon confirmed that the axons would sprout and regenerate into the muscle without neuroma formation in at least 80% of patients without prolonging the surgery[34,35]. Possible pitfalls can occur if the chosen muscle is too close to the skin, the muscle is too big or there is another nerve contributing to the pain. The nerve can also be implanted in bone or vein, but these "passive" techniques do not address the regenerative potential of the nerve stump and can result in recurrence of symptoms[19,20].

Nerve capping

Nerve capping is another passive technique for end-neuroma treatment that has shown poorer results. Different synthetic materials or vein can be used to cap the end of the nerve so that painful regrowth of the nerve can be reduced. More recent studies have been focused on nerve capping and selecting a conduit for treatment of neuroma in continuity, not for end-neuroma[16].

End-to-end nerve coaptation

Depending on the level of amputation and the nerves involved, nerve coaptation can be done between different nerves epineurally or between fascicles in the same nerve (centro-central neurorrhaphy)[16]. Therefore, it is expected that repairing "like to like" tissue as a basic principle in plastic surgery, the nerve stump covered with regenerated epineurium will return the nerve to its physiological state[32-33]. For example, if the sciatic nerve should be transected during amputation, the level of bifurcation should be identified and the common peroneal and tibial nerve should be transected, followed by end-to-end neurorrhaphy between nerves[1]. A

small number of studies showed better results using this treatment compared to the traction neurectomy.

Targeted muscle reinnervation (TMR)

Introduced by Kuiken, Dumanian and Aszmann, targeted muscle reinnervation includes residual peripheral nerve transfer to a smaller nerve branch after this nerve is transected near the target muscle that is denervated but vascularized. The goal is that the axons of the different motor nerve make new connections and reorganize the target muscles[21]. Originally TMR was designed for improving bionic device control in upper extremity amputees as biologic amplifiers of the nerve's signals. It was incidentally found that TMR can prevent neuroma formation especially compared to standard techniques, and it can be taken into consideration as a primary approach for neuroma treatment[24]. The coaptation of the residual and recipient nerve promotes organized nerve regeneration into the denervated muscle in contrast to the disorganized mass of axons leading to neuroma formation[18,23]. The biggest concern about this procedure was the size mismatch between the nerves, but studies showed this disproportion only provided hyperinnervation leading to reinnervated target muscles. TMR adds about 20-45 minutes per nerve to the operative time with or without using a microscope.

Regenerative peripheral nerve interface (RPNI)

The RPNI is a simple surgical procedure pioneered by Cederna, and was initially described as a neuroprosthetic control strategy used in upper extremity amputees to amplify the peripheral nerve signals to control a bionic hand. Studies in the field of bioprosthetics examining the formation of new neuromuscular junctions also reported the absence of neuroma formation[13-14]. Those results led to performing RPNIs for treatment of symptomatic neuromas but also as a prophylactic procedure at the time of amputation. A RPNI includes implantation of the distal end of a nerve that has been transected into an autologous free skeletal muscle graft. The graft can be harvested from a viable muscle from the amputated leg or the residual limb. Depending on whether it is an above- or below-knee amputation, usual donor muscles are the *gastrocnemius* muscle or *vastus lateralis*. The dimensions of the devascularized and denervated grafts are 3 x 1.5 x 1 cm and are harvested along the axis of muscle fibers. The transected end of the nerve is placed on the graft and secured with two 6-0 non-absorbable monofilament sutures followed by wrapping the muscle around the nerve and securing it with epimysial sutures[13-14] (Figure 2). The survival of the graft is based on imbibition, inosculation and revascularization and hence, the graft should not be too big or too thick to avoid necrosis. The goal of the RPNI is to provide a target for the distal end of the nerve or simply speaking – to give the nerve something to do. Research showed that RPNI is a stable structure, leads to successful reinnervation that reduces neuroma formation and consequently postamputation pain. After RPNI formation, the rest of the amputation procedure does not differ from the classical technique taking in regard to protect the RPNI from the surface. If the transected nerve is too big, as the sciatic nerve, intraneural dissection is performed and the nerve is divided in two or three fascicles and an RPNI is created for each fascicle. This technique does not delay the operative time significantly; it usually takes 7-10 minutes to create each RPNI[13]. Possible surgical complications do not differ from the classic amputation technique and can be safely used in patients with comorbidities such as diabetes, osteomyelitis, peripheral vascular disease or smokers. The results of recent studies have confirmed the benefits of RPNI surgery that include prevention of the process of central sensitization, lowering postoperative residual limb pain and phantom limb pain that leads to prompt rehabilitation and usage of a prosthetic device [25-27].

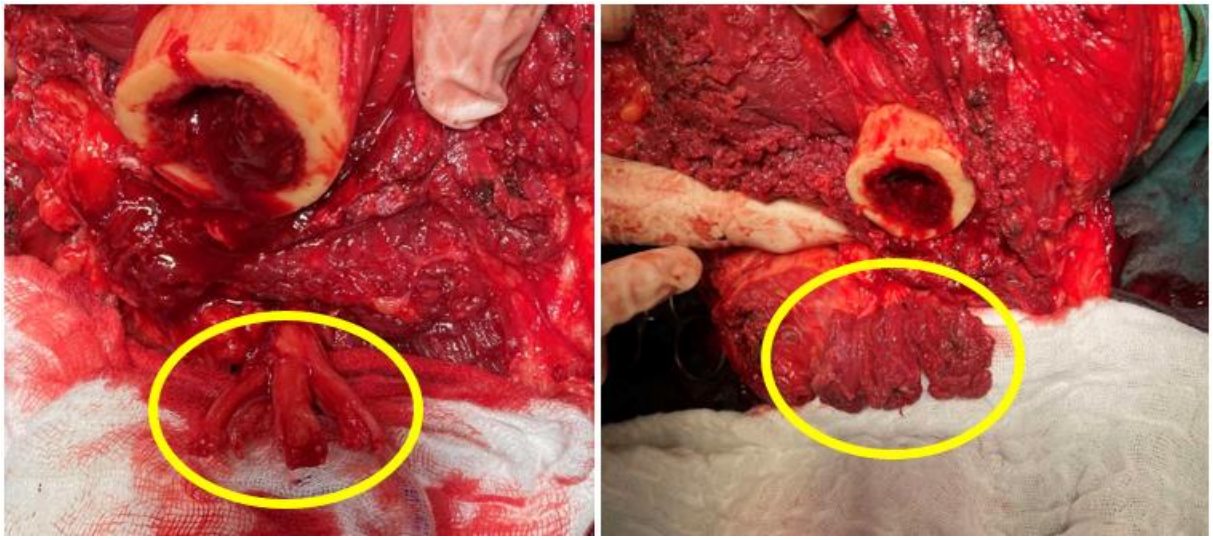

Fig. 2. Intraneural dissection of the sciatic nerve and three RPNIs created

TMR or RPNI, TMR and RPNI - TMRpni

TMR and RPNI are novel techniques that have yielded excellent results such as prevention of neuroma formation, providing a target into which the transected nerve can regenerate[17]. Any one of these strategies can be used prophylactically at the time of amputation and when prevention is possible, it is always a better solution than postamputation pain treatment and management. To date, there is no thorough research that can compare the two techniques. The advantages of RPNI include minimal technical requirement; microsurgical skills are not necessary and it is a simple procedure that does not delay the surgical time[31]. There is no need for nerve mobilization and there is minimal or no harvest site morbidity when the graft is taken from the amputated extremity. Main concerns are viability of the graft and if there are sufficient neuromuscular junctions available in the graft. On the other hand, TMR theoretically suggests ideal regenerative environment but causes muscle denervation. The technical complexity is bigger and the need for nerve mobilization and surgical exposure is greater. TMRpni is a combination of the two techniques, which basically means using and RPNI graft with a TMR technique. This surgical strategy is used when a larger donor nerve is coapted to a much smaller motor target so that the free graft will be a target for any escaped donor axons [28-30]. Due to the limitation to compare the efficacy of both techniques, it still remains the surgeon's preference.

Conclusion

Although there are not enough studies that can show unified results regarding treatment or prevention of postamputation pain and neuroma formation, most of the presented techniques can be taken into consideration for patients with major lower limb amputation. Relevant factors are the expertise and skills of the surgeon and the medical condition of the patient at the time of surgery, but overall each technique presents with a level of effectiveness.

TMR and RPNI are modern strategies that can prevent phantom limb pain and residual limb pain, thus leading to further innovation in amputation surgery.

To conclude, a prophylactic surgical technique should be performed at the time of amputation to prevent postamputation pain, thus enhancing patients' quality of life and early rehabilitation.

Conflict of interest statement. None declared.

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