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DIGEST AND REVIEWS

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Methods of reinnervation after amputationsin patients with the consequences of combat injuries (literature review)

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The full-scale aggression of the Russian Federation against Ukraine has significantly increased the number of cases and the structure of factors leading to the performance of such surgical interventions as amputation. There are no reliable statistics on the number of limb amputations performed since the beginning of the full-scale invasion of the Russian Federation into the territory of Ukraine due to objective factors, however, according to preliminary estimates, their number exceeds 50 thousand people. One of the significant problems after limb amputations is pain syndrome, which is observed in 60 to 86 % of patients, which is divided into two types: residual limb pain (RLP) and phantom limb pain (PLP). This problem is relevant for modern world orthopedics and traumatology, the solution of which requires a multidisciplinary approach, and further study will allow to improve treatment tactics and improve the final results. The purpose was to determine the optimal surgical technologies for performing amputations in victims with combat injuries and analyze modern reinnervation methods by studying literary sources. Methods. An assessment of modern publications, systematic reviews, and current recommendations published recently was conducted, which are devoted to methods of treatment and prevention of neuroma formation in limb amputations. A search was conducted in the PubMed, Scopus, Web of Science, and Google Scholar, databases using the following terms: «amputation», «RPNI», «VDMT», «TMR», «phantom», «clinical effectiveness», «post-amputation pain», «BNA», «ANA», «RLP», «PLP», «stump neuroma», «symptomatic neuroma», «pain neuroma». Relevant articles were included after reading the full text and determining the necessary parameters. The review was prepared in accordance with the recommendations of the "Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines". Conclusions. The results of scientific studies indicate that reinnervation methods (TMR, RPNI, VDMT) are clinically more effective than traditional amputation. These methods can be used with equal effectiveness both for the prevention of late post-amputation complications (symptomatic neuromas, phantom limb pain, residual limb pain) and for their treatment.

Повномасштабна агресія російської федерації проти України суттєво збільшила кількість випадків і змінила показання чинників щодо виконання таких оперативних втручань, як ампутація. Достеменних статистичних даних стосовно кількості проведених ампутацій кінцівок із початку повномасштабного вторгнення немає через об'єктивні фактори, проте за попередніми підрахунками їхня кількість перевищує 50 000 осіб. Однією зі суттєвих проблем після ампутацій кінцівок є больовий синдром, який спостерігається від 60 до 86 % пацієнтів та поділяється на два типи: біль у куксі (RLP — Residual Limb Pain) і фантомний біль у кінцівках (PLP — Phantom Limb Pain). Це питання є актуальним для сучасної світової ортопедії і травматології, його розв'язання потребує мультидисциплінарного підходу, а подальше вивчення дозволить удосконалити лікувальну тактику та покращити кінцеві результати. Мета. Визначити оптимальні хірургічні технології проведення ампутацій у постраждалих із бойовими ураженнями та проаналізувати сучасні реіннерваційні способи шляхом вивчення літературних джерел. Методи. Проведено дослідження сучасних публікацій, системних оглядів, діючих рекомендацій стосовно методик лікування та профілактики утворення невром за ампутацій кінцівок. Здійснено пошук у базах даних PubMed, Scopus, Web of Science та Google Sholar, за ключовими словами: «amputation», «RPNI», «VDMT», «TMR», «phantom», «clinical effectiveness», «post-amputation pain», «BNA», «ANA», «RLP», «PLP», «stump neuroma», «symptomatic neuroma», «pain neuroma». Огляд підготовлений згідно з рекомендаціями «Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines». Висновки. Результати наукових досліджень указують, що реіннерваційні способи (TMR, RPNI, VDMT) є клінічно ефективніші як порівняти з традиційною ампутацією. Ці методики з однаковою продуктивністю можуть застосовуватись як для профілактики пізніх постампутаційних ускладнень (симптоматичні невроми, фантомний або біль безпосередньо в куксі), так і під час їхнього лікування. Ключові слова. Поліструктурні ушкодження кінцівок, ампутації, способи реіннервації.

Keywords. Polystructural limb injuries, amputations, reinnervation methods

Introduction

Amputation is a surgical procedure that involves the removal of a limb. The main causes are vascular disease, diabetes, and peripheral arterial disease (54 %), trauma (45 %), and cancer (approximately 2 %). Studies using data from the Nationwide Inpatient Sample, the largest inpatient database in the United States, have found that nearly 115,000 people require lower limb amputations each year [1, 2, 20].

Military conflicts, often involving the deployment of high-energy weapons, frequently lead to severe polystructural limb injuries in over 50 % of cases. Such extensive damage renders modern reconstructive surgery insufficient in achieving positive functional outcomes for these victims. Thus, according to publications on wounded participants of the Joint Forces Anti-Terrorist Operation (ATO/JFO), the main cause of amputation was mine-explosive trauma (MET) in 78.4 % of cases. There are no reliable statistical values regarding the number of limb amputations performed since the beginning of the full-scale invasion of the Russian Federation into the territory of Ukraine due to objective factors, but according to preliminary estimates, there are more than 50 thousand people [1].

One of the significant problems after limb amputations is pain syndrome, which is observed from 60 to 86% of patients and is divided into two types: residual limb pain (RLP) and phantom limb pain (PLP) [9].

Phantom limb pain (PLP) is clinically recognized as the sensation of pain or discomfort in an absent limb, and it can present across a broad clinical spectrum with varying degrees of severity. Formerly known as "stump pain", it is pain originating from the actual site of the amputated limb, most often occurring in the early postoperative period and tending to disappear during wound healing. In the majority of instances, these conditions occur together. Factors for the development of RLP include neuroma formation, nerve compression, ischemia, skin damage, or infection [6, 12].

PLP and RLP are relevant issues from the point of view of epidemiology and therapeutic difficulties. It is known that 95 % of patients experience pain associated with amputation, with 79.9 % experiencing phantom pain and 67.7 % experiencing pain directly in the stump [8].

Taking into account the problems outlined, determining the optimal surgical techniques for amputation in general and the treatment of nerve structures in particular is a relevant issue in modern orthopedics.

Purpose: to determine the optimal surgical techniques for performing amputations in combat-wounded patients and to analyze modern reinnervation techniques by studying literature sources.

Material and Methods

An analysis of modern publications, systematic reviews, and current recommendations on methods of treatment and prevention of neuroma formation in case of limb amputations was conducted. A search was conducted in the PubMed, Scopus, Web of Science, and Google Scholar databases using the following keywords: "amputation", "RPNI", "VDMT", "TMR", "phantom", "clinical effectiveness", "post-amputation pain", "BNA", "ANA", "RLP", "PLP", "stump neuroma", "symptomatic neuroma", "pain neuroma". The review was prepared in accordance with the "Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines".

Inclusion criteria: 1) limb amputations in patients due to combat trauma; 2) late post-amputation complications, such as neuroma, phantom pain, stump pain, scar innervation; 3) use of reinnervation techniques: VDMT, TMR, RPNI; 4) articles with evidence levels I–IV; 5) follow-up duration of at least one year.

Exclusion criteria: 1) amputations due to non-combat trauma; 2) reviews, abstracts or articles that did not include sufficient data; 3) non-standardized reinnervation techniques.

According to the specified criteria, two independent researchers checked the search results by title, abstract and full text. The obtained data included: first author, level of evidence, year of publication, study design, type of amputation, number and age of patients, reinnervation techniques.

Meta-analysis was performed using the Meta package to generate risk ratios for categorical outcomes, mean differences for continuous outcomes, and 95% confidence intervals (CIs).

The results of studies on the development of symptomatic neuromas and phantom pain syndrome in cases of upper and lower limb amputations are presented in Table 3.

The results of prevention and treatment of late local post-amputation complications are shown in Table 4.

The results of the study on the risk of reoperation after performing reinnervation surgical methods and traditional amputation are given in Table 5.

Discussion

Neuroma develops from a transected peripheral nerve that regenerates and lacks a distal target for

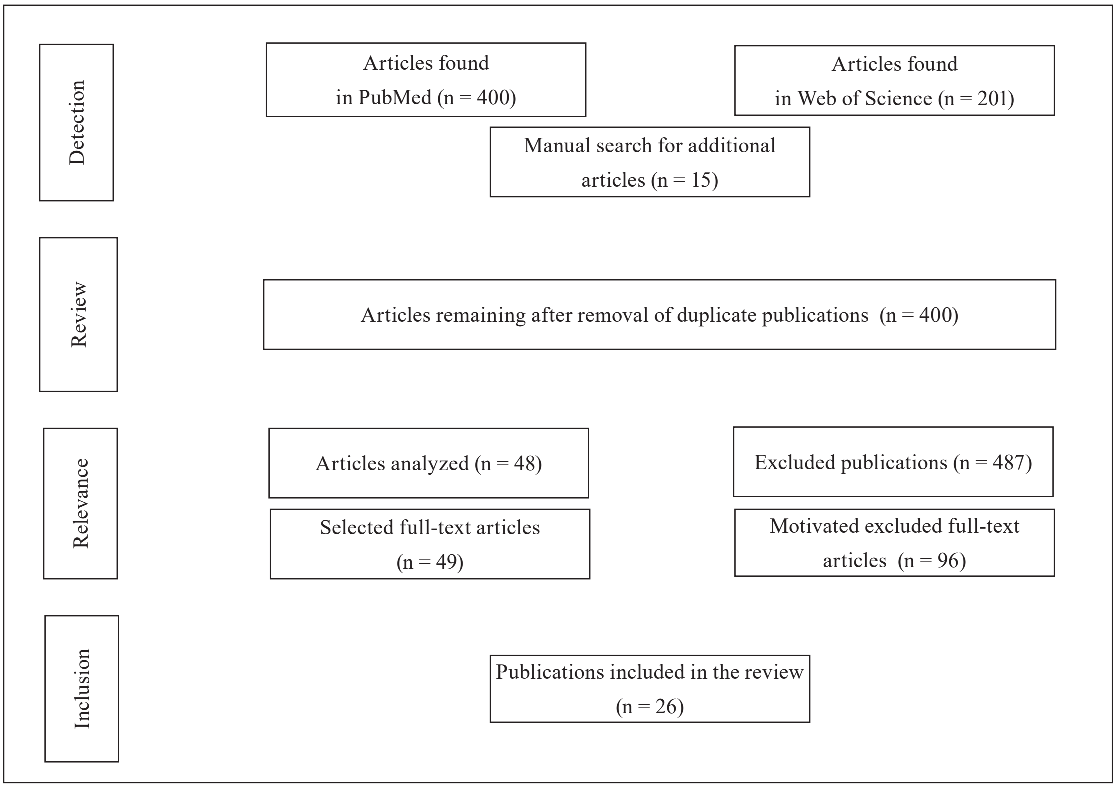

Figure. Flowchart of article selection for the study

Table 1

Assessment of reinnervation surgical techniques

Author, year, country	Characteristics of models	Method of reinnervation
C. S. Best et al., 2024, USA [4]	Lower limb amputations at different levels	RPNI
C. A. Kubiak et al., 2021, USA [14]	Lower limb amputations at different levels	RPNI
J. B. Bowen et al., 2019, USA [5]	Below-the-knee amputations (BNA)	TMR
S. Pejkova et al., 2022, Northern Macedonia [22]	Lower limb amputations at different levels	RPNI
F. Mereu et al., 2021, Italy [19]	Upper limb amputations	TMR
Z. W. Fulton et al., 2022, USA [10]	Upper and lower limb amputations	TMR
P. J. Hanwright et al., 2023, USA [11]	Lower limb amputations	VDMT

Table 2

Analysis of clinical outcomes of patient treatment using various reinnervation techniques

Author, year, country	Amputation	Method of reinnervation		Study design
V. Suresh, et al., 2023, USA [25]	Upper limbs	VDMT — 9	Traditional amputation — 4	Retrospective
Z. Lin et al., 2023, China [17]	Lower limbs	RPNI — 7	Traditional amputation — 7	Retrospective
C. A. Kubiak et al., 2019, USA [15]	Upper and lower limbs	RPNI — 45	Traditional amputation — 45	Randomized
E. Pettersen et al., 2024, USA [23]	Upper and lower limbs	TMR — 37 RPNI — 37	Traditional amputation — 37	Prospective

reinnervation. Symptomatic neuromas are a common cause of post-amputation pain that can result in significant disability in young adults [4].

Although many interventions have been proposed for the treatment of symptomatic neuromas, conventional techniques result in a high recurrence rate,

Table 3

Results of studies on the development of symptomatic neuromas and phantom pain syndrome in limb amputations

Author, year, country	Study characteristics	Summary
C. A. Kubiak et al., 2019, USA [15]	The results of treatment of patients who underwent amputation with and without the RPNI method were analyzed.	RPNI in individuals with limb amputations resulted in a lower incidence of both symptomatic neuromas and phantom limb pain compared with a control group who underwent amputation without RPNI. This suggests that prevention of symptomatic neuromas after amputation may reduce central pain mechanisms that, in turn, lead to phantom limb pain.
Z. Lin et al., 2023, China [17]	The indicators of individuals with lower limb amputations are presented. Clinical data were collected including general information, pathology of the underlying disease, history of surgical treatment, level of neurotomy, pain scales: Numeric Rating Scale (NRS) and Manchester Foot Pain and Disability Index (MFPDI). 3 months after amputation, the transverse diameter, anterior-posterior diameter and cross-sectional area of the stump neuroma were measured using ultrasound and compared with normal nerves of the opposite limb at the same level.	The NRS and MFPDI scores of patients in the RPNI group were significantly lower than those in the traditional amputation group and decreased with increasing follow-up time, indicating that RPNI may reduce symptomatic pain behind the nerve.
A. L. O'Brien et al., 2022, USA [21]	Data from patients undergoing TMR after limb amputation were analyzed. Outcomes included patient-reported severity of PLP and RLP, measured by a numerical rating scale (NRS). Secondary outcomes were compiled into patient-reported outcome information system (PROMIS) questionnaires.	At 3 months postoperatively, all PLP and RLP outcomes were compared with previously reported data, which demonstrated superiority over amputations without TMR. Mixed-model linear regression analysis revealed that PLP severity scores on the NRS scale continued to improve over the study period ($p = 0.022$). The remaining outcomes for RLP severity and PROMIS quality of life scores demonstrated that these scores remained stable over the study period ($p > 0.05$). TMR is an effective surgical procedure that improves the chances of reducing RLP and PLP when performed at the time of amputation
V. Suresh et al., 2023, USA [25]	The consequences of treating patients who underwent upper limb amputation using the VDMT method as a preventive measure against neuroma formation are considered.	The mean follow-up period was (5.6 ± 4.1) months (CI 0.5–13.2). The mean postoperative pain score was 1.1 (CI 0–8). This study demonstrated favorable short-term outcomes in individuals undergoing VDMT of the upper extremity.

and there remains considerable disagreement about the most optimal treatment and prevention strategy for PLP and RLP [14]. Reinnervation techniques such as RPNI (Regenerative Peripheral Nerve Interface), VDMT (vascularized denervated muscle target), TMR (Targeted Muscle Reinnervation) are aimed at preventing specific neuropathic pain after amputation [7].

The RPNI technique is performed by implanting the distal end of the transected peripheral nerve into a free, nonvascularized skeletal muscle graft. The neuroma or free end of the affected nerve is identified, the nerve is transected, and the nerve is mobilized proximally. A free muscle graft is harvested directly from the stump wound or from another anatomical site. The end of each transected peripheral

Table 4

Results of prevention and treatment of late local post-amputation complications (occurrence of symptomatic post-amputation neuromas, PLP, RLP)

Author, year, country	Flynn criterion, %				Summary (compared to traditional amputation)
	E	G	S	US	
C. S. Best et al., 2024, USA [4]	91.2 (RPNI) 7.1 (TA)	5.4 (RPNI) 5.3 (TA)	2.2 (RPNI) 16.2 (TA)	1.2 (RPNI) 71.4 (TA)	RPNI provides a reduction in the incidence of both symptomatic neuromas and phantom limb pain
C. A. Kubiak et al., 2021, USA [15]	93.2 (RPNI) 2.3 (TA)	5.2 (RPNI) 17.3 (TA)	1.6 (RPNI) 12.1 (TA)	— 68.3 (TA)	RPNI provides a lower incidence of symptomatic neuromas and phantom limb pain
J. B. Bowen et al., 2019, USA [5]	72.4 (TMR) 32.1 (TA)	22.6 (TMR) 58.6 (TA)	5.0 (TMR) 9.3 (TA)	— —	TMR showed better clinical results: the incidence of symptomatic neuromas was reduced, as well as the intensity of phantom pain
Z. Lin et al., 2023, China [17]	81.2 (RPNI) 2.9 (TA)	8.4 (RPNI) 67.3 (TA)	10.4 (RPNI) 22.8 (TA)	— 7.0 (TA)	Pain syndrome (RLP, PLP) NRS and MFPDI scores of patients in the RPNI group were significantly lower
A. L. O'Brien et al., 2022, USA [21]	84.5 (TMR) 3.8 (TA)	14.2 (TMR) 29.1 (TA)	1.3 (TMR) 1.7 (TA)	— 65.4 (TA)	TMR showed better clinical results: PLP severity scores on the NRS scale were lower
V. Suresh et al., 2023, USA [25]	74.1 (VDMT) 15.3 (TA)	22.5 (VDMT) 13.5 (TA)	3.4 (VDMT) 68.4 (TA)	— 2.8 (TA)	VDMT provides a lower incidence of symptomatic neuromas, as well as a reduction in PLP (as measured by the MFPDI scale)

Notes: E — excellent; G — good; S — satisfactory; US — unsatisfactory.

Table 5

Risk of repeat surgical interventions after performing reinnervation surgical techniques (TMR, VDMT, RPNI) and traditional amputation

Author, year, country	Risk of repeated surgical interventions according to the Flynn criterion, %		Summary
	traditional amputation	reinnervation techniques (RPNI, VDMT, TMR)	
C. S. Best et al., 2024, USA [4]	37.2	2.4	Provide a lower risk of re-surgery for late post-amputation complications (symptomatic neuromas)
P. J. Hanwright et al., 2023, USA [11]	27.4	2.6	Leads to a lower risk of reoperation for late post-amputation complications (PLP, RLP)
S. Pejkova et al., 2022, Northern Macedonia [22]	25.1	1.9	Cause a lower risk of re-surgery for late post-amputation complications (symptomatic neuromas)

nerve is implanted into the center of the free muscle graft using 6–0 nonabsorbable suture. RPNI can be performed directly at the time of amputation or as an elective procedure at any time after surgery. The skeletal muscle graft should ideally be approximately 35 mm long, 20 mm wide, and 5 mm thick to ensure survival and prevent central necrosis. Collection can be done using curved Mayo scissors. The end of the transected peripheral nerve should be implanted parallel to the direction of the muscle fibers, and the epineurium should be sutured to the free muscle graft in 1 or 2 places. A single suture should be used to secure the distal end of the epineurium to the middle of the muscle graft bed. It is then wrapped around the nerve in a cylinder with suture fixation. The RPNI should be avoided in the area of the load-bearing surface of the stump. It should be deep in the muscle tissue, away from the subcutaneous tissue and dermis. For large nerves, intraneural dissection into separate structures should be performed to create several (usually 2–4) separate RPNIs to avoid too many regenerating

Table 6

Results of the quality of life index study (PROMIS) after reinnervation surgical techniques (TMR, VDMT, RPNI) and traditional amputation

Author, year, country	Flynn criterion, %				Conclusion
	E	G	S	US	
A. L. O'Brien et al., 2022, USA [21]	74.5* 52.1**	19.3* 2.1**	3.8* 44.8**	2.4* 1.0**	PROMIS scores in patients after reinnervation surgical procedures are higher than those after traditional amputation
M. Byl et al., 2024, USA [6]	72.1* 48.4 **	24.1* 14.9**	1.2* 32.3**	2.6* 4.4**	
M. Diers et al., 2022, USA [8]	83.6* 22.1**	12.4* 24.6**	2.4* 42.3**	1.6* 11.0**	

Notes: E — excellent; G — good; S — satisfactory; US — unsatisfactory; * — reinnervation techniques (RPNI, VDMT, TMR); ** — traditional amputation.

axons in a single free muscle graft. The advantage of RPNI is its technical simplicity and versatility.

Regeneration occurs by direct neurotization of the muscle graft. Given the understanding that neuromas form when regenerating axons lack end organs for reinnervation, any strategy that reduces the number of untargeted axons in the residual limb should help minimize symptomatic neuromas. The use of free muscle grafts offers a large pool of denervated muscle targets for nerve axon regeneration and facilitates the restoration of neuromuscular junctions without compromising denervation of other stump muscles [4].

Because RPNIs are nonvascularized muscle grafts, they must initially survive by diffusion of nutrients from the surrounding wound bed until revascularization. If they are too large to allow sufficient diffusion of nutrients, necrosis will occur. Even when a small muscle graft is placed in an ideal wound bed, some degree of fibrosis and muscle resorption is expected during the healing process. This raises questions about whether RPNI provides a sufficient target to receive all axons regenerating from the peripheral nerve stump, especially when the technique is used on large-caliber nerves. Like RPNI, VDMTs are used to redirect regenerating axons from the transected nerve into the denervated muscle to prevent neuroma formation. By providing a vascularized muscle target that is reinnervated by direct neurotization, VDMT has advantages over other surgical options. Performing VDMT involves first elevating a muscle island on a vascular pedicle in such a way that it is denervated while remaining vascularized. The nerve stump is then implanted into the denervated muscle flap or wrapped around it in a manner similar to RPNI. This technique is similar to RPNI, but unlike the latter, it allows the use of larger muscle grafts without the risk of necrosis. VDMT is essentially vascularized RPNI [25].

TMR is a surgical technique in which peripheral nerve stumps are sutured to the adjacent muscle branch. These nerve transfers provide a pathway for axonal growth, limiting the disorganized regeneration of nerve endings that leads to neuroma formation. This method has also been used to improve control of a bionic prosthesis by increasing the number of independent muscle signals [3, 26].

Targeted sensory reinnervation (TSR) is performed using a similar surgical principle, in which a peripheral sensory nerve stump is sutured to a small cutaneous branch or simply implanted into the subcutaneous fat for "neurogenic capture" of skin receptors. TSR can be used to treat symptomatic neuromas, although this is not its primary purpose. It is mainly used to improve sensory response from the prosthesis. TSR is currently not used more frequently for the treatment and prevention of symptomatic neuromas than other described techniques and requires further research.

According to the results of the study by C. S. Best et al., the RPNI method for the treatment of pain after amputation showed favorable results, with a significant reduction in pain during neuroma and phantom pain syndrome approximately 7 months after surgery. Neuroma pain scores decreased by 71 %, and phantom pain scores on the visual analog scale (VAS) decreased by 53 %.

Prophylactic RPNI is also associated with a significantly lower incidence of symptomatic neuromas (0 vs. 13.3 %) and lower levels of phantom limb pain (51.1 vs. 91.1 %) compared with patients who underwent conventional amputation [4].

In a study of primary and secondary TMR by Z. W. Fulton et al., the majority of patients experienced resolution of neuroma pain (86.2 %) and overall reduction/absence of pain (90.7 %). No differences were found between primary and secondary TMR. Preliminary data suggest that TMR is effective in preventing or treating pain in amputees, whether used in the acute or delayed period [10].

According to V. Suresh et al., published in 2023, of the 9 subjects included in a retrospective study of VDMT, 7 underwent VDMT surgery as a prophylactic measure against neuroma formation, and 2 had symptomatic neuromas treated with VDMT. The mean follow-up period was (5.6 ± 4.1) months. The mean postoperative pain score was 1–2 points on the VAS scale [25]. J. B. Bowen et al. conducted an analysis that included 17 studies, 14 of which evaluated TMR (366 patients) and 3 evaluated RPNI (75 patients). They determined that TMR and RPNI for the treatment of pain reduced neuroma in 75–100 % of patients and phantom limb pain in 45–80% of cases. When TMR or RPNI was performed prophylactically, many patients reported no residual limb pain (48–100%) or phantom limb pain (45–87 %) at follow-up. Complication rates ranged from 13 to 31 %, with delayed wound healing being the most common [5].

Analysis of the results of comparisons of traditional amputation and reinnervation techniques in amputation surgery indicates that the disadvantage of the traditional method is the increased risk of late complications (symptomatic neuromas, phantom and stump pain) [4, 5, 14, 17, 21].

Reinnervation techniques have more advantages for the treatment of PLP and RLP, while allowing patients with amputated limbs to return to daily activities, improve quality of life and increase the duration of use of prostheses without correction. Recent studies in the field of reinnervation techniques demonstrate great potential to set a new standard in amputation surgery [4, 10, 14, 17, 25].

The described reinnervation techniques have a significant impact on prosthetic repair, providing better integration and interaction with the nervous system, which, in turn, increases the functionality, comfort and quality of life of patients. These technologies allow better adaptation to their new living conditions, improve the accuracy of prosthesis control and reduce psychological stress from the loss of a limb.

The presented analysis of literature sources has certain limitations: the observation period in the analyzed studies at the time of writing the article does not exceed 3–4 years, considering that the results obtained may differ from the indicators revealed over a longer period of observation.

Conclusions

The results of scientific studies indicate that reinnervation techniques (RPNI, VDMT, TMR) are clinically more effective compared to traditional amputation. These techniques can be used both for the prevention of late post-amputation complications (symptomatic neuromas, phantom and pain directly in the stump), and for their treatment.

Clinical results based on questionnaire data (PROMIS, VASH, MFPDI, NRS), imaging studies and functional data indicate that reinnervation techniques prevent the development of late post-amputation complications, which lead to a decrease in the frequency of repeated surgical interventions. At the same time, the quality of life index remains consistently high after any of the above reinnervation techniques, in contrast to traditional amputation, which is important for the comfortable integration of the patient into everyday life.

Modern reinnervation techniques used in amputation surgery play an important role in improving the functionality and quality of life of people who have undergone limb amputation, especially when it comes to prosthetic repair.

RPNI, VDMT and TMR allow to reduce the feeling of pain and discomfort directly in the stump, as well as to minimize the level of phantom pain during the use of the prosthesis, because the nerves receive new paths for transmitting impulses, as a result, control over the prosthesis improves, which has a positive psychological effect on patients, as it gives them a feeling of returning to normal life and provides greater independence in everyday activities.

Conflict of interest. The authors declare the absence of a conflict of interest.

Prospects for further research. The direction of the conducted research meets the challenges of today. The use of modern treatment methods allows to improve the quality of life of victims and requires further development, improvement and implementation of reinnervation technologies in amputation surgery.

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Authors' contribution. Buryanov O. A. — concept and design of the study; Smyk O. O. — systematization of literary sources, collection and processing of materials, analysis of the results obtained, drafting the articles; Salenko M. S. — selection and analysis of references, drafting the article.

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METHODS OF REINNERVATION AFTER AMPUTATIONS IN PATIENTS WITH THE CONSEQUENCES OF COMBAT INJURIES (LITERATURE REVIEW)

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