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Peripheral Nerve

Evaluation of Processed Nerve Allograft in Peripheral Nerve Surgery: A Systematic Review and Critical Appraisal

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Background: Peripheral nerve injuries cause substantial problems when not treated properly. A specific problem is reconstruction of nerve defects, which can be treated in different ways. This study aimed to systematically review whether processed nerve allograft (PNA) is justified in reconstruction of a nerve defect in patients after posttraumatic or iatrogenic peripheral nerve injury and to compare PNA with other established methods.

Methods: A systematic review with a focused question, PICO (patient, intervention, comparison, outcome) and constraints, was performed. A structured literature search, including several databases, was done to evaluate the existing evidence for outcomes and postoperative complications related to PNA. The certainty of evidence was classified according to Grading of Recommendations, Assessment, Development and Evaluations.

Results: No conclusions, concerning differences in outcome of nerve reconstruction using PNA compared with the use of nerve autograft or conduits, could be drawn. The level of certainty for all evaluated outcomes was very low (⨁◯◯◯). Most published studies lack a control group to patients treated with PNA; being only descriptive, making it difficult to compare PNA with established methods without substantial risk of bias. For studies including a control group, the scientific evidence was of very low certainty, due to a low number of included patients, and large, undefined loss of patients during follow-up, rendering a high risk of bias. Finally, the authors often had financial disclosures.

Conclusion: Properly conducted randomized controlled trial studies on the use of PNA in reconstruction of peripheral nerve injuries are needed to establish recommendations in clinical practice. *(Plast Reconstr Surg Glob Open 2023; 11:e5088; doi: 10.1097/GOX.0000000000005088; Published online 27 June 2023.)*

INTRODUCTION

Injury to the peripheral nerve can occur after a variety of traumas. Injury to one or several digital nerves is the most common peripheral nerve injury (incidence 6.2/100,000 inhabitants/year; men are more often affected than women[1,2]), where incidence rates are similar in Sweden and Finland.[3] Depending on which nerve is injured and the extent of the injury, the consequences can lead to a varying, sometimes severe, disability with a risk of lifelong pain for the individual. A nerve injury is also costly for the society, as they mainly affect younger individuals with a risk for long periods of sick leave or permanent inability to work.[4–7] Attempts to restore or improve function in the limb are important to facilitate return to work; improve quality of life; and avoid permanent disability and chronic conditions, such as neuropathic pain, after a peripheral nerve

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injury. This is also crucial for the society in view of health care costs.[5]

Restoration of function of the injured nerve can be performed by different surgical techniques,[8,9] where the primary end-to-end nerve suture, possible to be performed in about 80% of the cases,[10,11] requires tension-free repair.[10,12] In complex injuries, with an extensive nerve defect or when the nerve repair is delayed, different techniques are used to bridge the defect. In contrast, a neuroma may be the consequence if a nerve is not repaired or reconstructed,[13] causing major problems with neuropathic pain, discomfort, and cold sensitivity for the affected individual.[14] Neuroma formation may be a demanding condition to treat, which potentially may develop into a complex regional pain syndrome (CRPS), that is, type 2 CRPS.

Bridging a nerve defect with autologous nerve grafts, such as the sural nerve, the terminal branch of the posterior interosseous nerve or other alternatives, is well established and considered to be the gold standard.[15–19] However, the use of an autologous nerve graft in nerve reconstruction has several possible disadvantages, which may be mainly related to residual problems from donor site[20–22] with risks of neuroma formation and subsequent symptoms[23,24] as well as risk for infections. Harvesting an autologous nerve graft prolongs the surgical procedure, implicating an increased need of resources. Finally, a mismatch in the size of the nerve graft with the size of the injured nerve may occur as well as a lack of enough graft material.

These potential obstacles for the use of autologous nerve grafts have prompted research and development of other alternatives for bridging peripheral nerve defects. One commonly used alternative is the use of commercially available collagen or polymer nerve conduits.[11,25] The ends of the injured nerve are inserted into the conduit, thereby facilitating the growth of the axons from the proximal nerve end toward the distal part of the nerve. Studies indicate that the results after nerve reconstruction with conduits work best when the defect is less than 3 cm.[25–29] Although not a gold standard treatment, as reconstruction with nerve autograft, nerve conduits have been on the market since the early 1990s, and extensive research on outcomes can be found in the literature.[11,30]

A newer, and principally interesting, alternative to autologous nerve grafting and artificial conduits is the use of a processed nerve allograft (PNA), which is a commercially available product manufactured and marketed as Avance Nerve Graft by Axogen Corporation (https://axogeninc.eu/avance-nerve-graft/).[31–34] The allograft is processed to remove all cell products, while preserving the three-dimensional microarchitecture to support the growing axons.[31,33–35] In recent years, studies have emerged showing suboptimal results after PNA treatment,[36–39] contributing to doubts in its suitability for treatment of all kinds of nerve defects.

The aim of our systematic review was to evaluate whether PNA is justified in reconstruction of nerve defects or surgical treatment of neuroma formation in patients with posttraumatic or iatrogenic peripheral nerve injuries and to compare PNA with the gold standard of treatment, reconstruction with nerve autograft, as well as with the well-established method of reconstruction with nerve conduits, based on existing, published evidence.

Takeaways

Question: Is processed nerve allograft (PNA) justified in reconstruction of a nerve defect in patients after a posttraumatic or iatrogenic peripheral nerve injury?

Findings: A systematic review with a focused question, PICO (patient, intervention, comparison, outcome) and constrains, was performed aiming to evaluate the existing evidence for outcomes and postoperative complications related to PNA. The level of certainty for all evaluated outcomes was very low (⨁◯◯◯).

Meaning: Properly conducted randomized controlled trial studies on the use of PNA in reconstruction of peripheral nerve injuries are needed to establish recommendations in clinical practice.

MATERIALS AND METHODS

Inclusion Criteria

In the initial literature search, we considered all types of study design and publication forms with publication dates from the year 2004 and later, in English, German, French, Spanish, and Scandinavian languages. Only studies regarding individuals over the age of 16 were included, with a follow-up time of 6 months or more. No limitations were set on a number of included individuals, or on those lost to follow-up. Inclusion criteria were defined in advance of data abstraction using the PICO framework.[40]

Patients

Included studies reported individuals with posttraumatic or iatrogenic injury to peripheral nerves.

Intervention

Study individuals had to be treated with surgery on peripheral nerves with a PNA.

Comparison

We analyzed all studies, including comparison to standard treatment in peripheral nerve surgery, involving direct suture, autologous nerve grafts, and the use of nerve conduits for peripheral nerve injury.

Outcome

Studies had to report at least one outcome measure postoperatively to be included in the analysis. These measurements included postoperative function measured by motor and sensory function, pain, and/or cold sensitivity; side effects or complications; measures for evaluation of rehabilitation; measurements on health-related quality of life, including return to work, studies, leisure activity, and/or other activities of daily living.

Literature Search

A systematic literature search was performed in March 2022 in the databases MEDLINE (Ovid interface; **See table**, **Supplemental Digital Content 1**, which shows Ovid MEDLINE search articles published 1946 through March 22, 2022, **http://links.lww.com/PRSGO/C626**), Embase (Ovid interface; **See table, Supplemental Digital Content 2**, which shows Ovid Embase search articles published 1974 through March 22, 2022, **http://links.lww.com/PRSGO/C627**), and Cochrane Library (**See table, Supplemental Digital Content 3,** which shows Cochrane Library search March 22, 2022, **http://links.lww.com/PRSGO/C628**).

Additional searches were made in Google Scholar and in the reference lists of relevant articles. Searches for ongoing clinical trials were conducted in the Clinical Trials (US National Library of Medicine) and International Clinical Trials Registry Platform (ICTRP, WHO) databases in March 2022 with the keyword "nerve allograft." Furthermore, searches were made for health technical assessment (HTA) reports on relevant websites in March 2022. (**See table, Supplemental Digital Content 4**, which shows search of HTA reports in the following sites using search words "allograft" and "nerve allograft," **http://links.lww.com/PRSGO/C629**.)

Based on title and abstract review, two information specialists independently made a first selection of articles, meeting the PICO and inclusion criteria. Disagreements were resolved by consensus procedure or assigned to an expert group, which included three experienced specialists in hand surgery (levels 4-5)[41] and one certified occupational therapist.

The literature search was updated through December 2022 to revise new articles, HTA reports, and ongoing studies published during the project period. (**See table, Supplemental Digital Content 5**, which shows PubMed search December 31, 2022, **http://links.lww.com/PRSGO/C630**.)

Selection and Data Extraction

The expert group reviewed the initially selected articles in full text for relevance. Relevant publications were subsequently evaluated for risk of bias (ROB). This was done according to HTA methodology.[42] Each assessment was made by at least two individuals from the project's expert group and an HTA supervisor, independently of each other. At all stages of the process, disagreements were resolved through a consensus procedure.

In the summarized ROB, evaluation was based on selection bias, treatment bias, assessment bias, dropout bias, reporting bias, and conflict of interest bias. The summarized ROB was stated as low, medium, or high. Only studies with medium and low ROB were included in the synthesis.

The certainty of evidence was assessed for each outcome using the Grading of Recommendations Assessment, Development and Evaluations (GRADE).[43] Each GRADE assessment was made in consensus by the expert group and the HTA supervisors.

Literature Search and Selection Process

A PRISMA flowchart of the search results and articles retrieved is shown in Figure 1. The systematic database searches resulted in a total of 8695 articles. Four additional articles were found by searching in Google Scholar, rendering a total of 8699 hits. After removing duplicates, 5603 unique items remained. The information specialists performed the first selection, based on the PICO criteria, using the screening tool Rayyan,[44] and the project group screened the 791 hits added after the updated database search. After this, 105 articles remained, and each abstract was examined by the expert group. Thirty-four original articles and nine systematic review articles were considered relevant for further assessment through full-text review. Following the ROB assessment, only five original articles met the PICO criteria and had a medium ROB, that is, being of medium quality and could be included in the review.

Twenty-nine original articles and nine systematic reviews were excluded from the quality review.

One article[45] was considered relevant, but was rejected because it was considered to have a high ROB. Three articles were discarded due to the wrong PICO (two with error I and one with error P) and incorrect study type, that is, uncontrolled studies not fulfilling the inclusion criteria. Another 25 articles were excluded for similar reasons, not fulfilling the inclusion criteria.

One systematic review was identified that did not comply with the present PICO criteria and was thus excluded.[46] In addition, eight systematic reviews were excluded due to the lack of a control group, rendering a high ROB.

The complete list of excluded articles, including the exclusion criteria, is found in **table**, **Supplemental Digital Content 6**, which shows excluded studies (original articles), **http://links.lww.com/PRSGO/C631** and **table, Supplemental Digital Content 7**, which shows excluded studies (systematic review articles), **http://links.lww.com/PRSGO/C632**.

RESULTS

The scientific literature regarding peripheral nerve surgery with PNA is extensive regarding case series and uncontrolled studies. However, for nonrandomized controlled trials (non-RCT) and RCTs, the scientific basis is very limited, including 23 individuals in one RCT and 495 individuals in four comparative controlled trials.

Description of Excluded Articles

Most of the excluded studies show positive outcomes after peripheral nerve reconstruction using PNA. Although most studies showed that PNA was a safe method for nerve reconstruction with some functional return after the procedure, four studies with negative results after PNA treatment were also identified.[36–39] These consisted of a case report with three patients from Finland, in which PNA surgery failed,[36] as well as a study with five case descriptions, where no functional recovery was seen after PNA treatment.[37] Another report with two patients, where

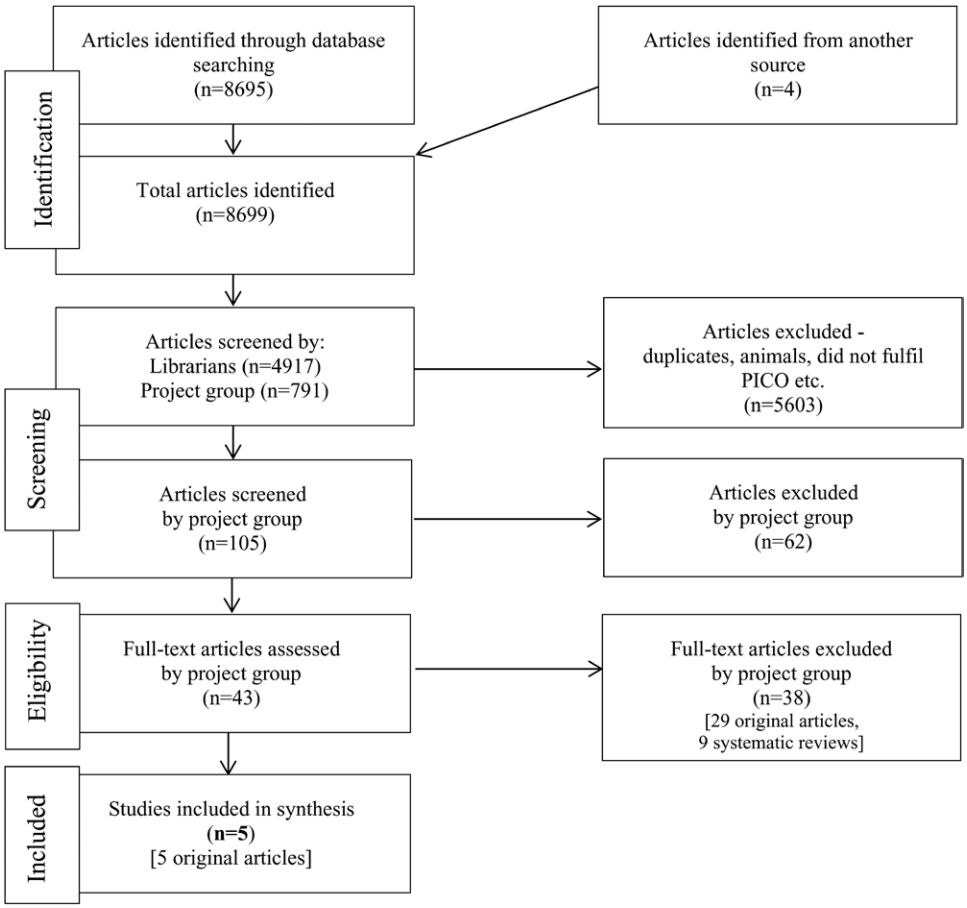

Fig. 1. PRISMA flow diagram for literature search and article inclusion concerning nerve allograft.

a histological, immunohistochemical analysis indicated failure of the PNA with loss of physiological microvascular architecture,[38] was identified as well as a retrospective case series including 14 patients with no motor or sensory improvement at 10 months follow-up.[39]

Six of the 26 uncontrolled studies are based on the RANGER register,[47] a database created by the Axogen Corporation and monitoring the use of PNA.

Lans et al[48] recently presented a systematic review and a meta-analysis, indicating that meaningful recovery rates do not differ significantly, regardless of gap length or nerve type when treated with autograft or allograft, and are significantly better than the meaningful recovery rates reported for conduits in short gap sensory nerves.

Description of Included Articles

Five original studies were considered relevant, with a medium ROB, and thus, were included in the synthesis. Four studies included individuals treated for digital nerve injuries,[49–52] whereas one study included individuals treated for digital nerve neuroma.[53] There were no studies judged to have a low ROB. The study design and the patient cohorts in the included studies were too heterogeneous for a mathematical synthesis with meta-analyses. The individual original studies were, therefore, combined through a narrative synthesis. An assessment was then made of the scientific certainty/reliability. The design and results of these studies are reported in Table 1. The level of certainty was very low, as shown in Table 2.

Results from Individual Studies, Compiled, and the Narrative Synthesis

Outcome Measure 1: Postoperative Function

Four studies included outcome measures reported for recovery of sensory function after surgery.[49–52]

The sensory recovery was reported as an average value (mm) for the static two-point discriminatory sensation (s2PD), as a measure of meaningful recovery using the British Medical Research Council scale, and as the perceived touch/pressure thresholds of Semmes Weinstein Monofilament Test. Three studies[49–51] showed that reconstruction with PNA gives a significantly better s2PD at follow-up, compared with direct nerve repair with sutures and reconstruction with nerve conduits. One study[51] also showed significantly better perception of touch in the PNA group than those treated with nerve conduits.

One of the studies[50] showed a majority of patients with statistically significant sensory recovery in the PNA group, whereas two other studies[51,52] did not show any difference in sensory recovery.

Self-reported postoperative function is assessed in two of the articles.[51,53] Means et al reported results of

Table 1. Design and Results of Included Studies

Study/Country	Design/Follow-up	Individuals/ Lost to Follow-up	Intervention	Comparison	Comments
			Results		
			Complication	Complication	
He et al 2015[49]/ China	Non-RCT, prospective/ 6 mo	152 individuals/ 7 individuals	72 hANG (defect > 10 mm)	81 direct repairs with sutures (defect < 5 mm)	
			Efficacy model, with assumption of a satisfaction rate of noninferiority standard of ±15%, where the noninferiority hypothesis was assumed to be proven even if the satisfaction rate of the test group was <15% of that of the control group. The 95% CI of subtraction for the satisfied rate (trial–control) for SW monofilament test at patient level −6.1 to 10.9%. For s2PD trial, control group satisfied rate 95% CI 2.4 (−11.4; 19.8). s2PD improved over time in intervention group. Average distance 12.8 ± 6 mm at 6 mo postoperative.		
			Combined good and excellent rate for s2PD of hANG for repairing 1–5 cm digital nerve defects was 65.3%.		
			6 mild pain in wound 3 mild redness 2 tenolysis	Not analyzed	
Leversedge et al 2020[50]/USA	Non-RCT, retrospective/ 10 mo	110 individuals/ 0 individuals	64 PNA Mean s2PD 9.7 ± 3.6 88% meaningful recovery	46 NC Mean s2PD 12.2 ± 4.0 61% meaningful recovery	Funding for the study was provided by AxoGen Corporation.
			Overall improvement in nerve function reported in 95% in PNA group versus 73% in conduit group		
			Revision rate of 3% by subject and 3% by nerve repair.	Revision rate of 7% by subject and 12% by nerve repair.	
Means et al 2016[51]/ USA	RCT/up to 12 mo	23 individuals/ 11 individuals	14 PNA Mean s2PD at 12 m: 5 ± 1 mm All returned some degree of s2PD	9 NC Mean s2PD: 8 ± 5 mm 75% returned some degree of s2PD	Not blinded
			DASH questionnaire, thermal discretion, and pain assessment scores at month 12 showed positive outcomes for both groups, and no statistical significance was found.		
			One infection	Two infections	
Lans et al 2020[53]/ USA	Non-RCT, retrospective/ up to 13 years. Median 7.6 years	91 individuals/ 62 individuals	2 PNA	10 nerve repair/reconstruction/ 9 neuroma excision and implantation/8 neuroma excision alone	Only 2 PNA Not blinded
			Higher PROMIS pain interference significantly associated with neuroma excision and excision and implantation Neuroma excision alone ($\beta = 0.9$, $P < 0.001$), and neuroma excision followed by implantation ($\beta = 0.6$, $P = 0.022$) independently associated with higher numeric rating scale for pain scores in multivariable analysis		
Rbia et al 2019[52]/ USA/Netherlands	Non-RCT, retrospective/ 12 mo	142 individuals/ 105 individuals	18 PNA Mean s2PD at 12m: 8.5 ± 3.7 mm	19 NC Mean s2PD at 12:9.8 ± 3.8 mm	Missing analysis of the dropouts No randomization of procedure, surgeon's choice
			No statistical significance was seen between groups regarding sensory recovery		
			One neuroma One individual with allodynia and CRPS	One infection	

NC, nerve conduit; PROMIS, Patient-Reported Outcomes Measurement Information System

Table 2. Level of Evidence according to GRADE

Grade Analysis	Outcome Measure	Quality	Inconsistency	Directness	Sparse or Imprecise	Reporting Bias	Strong or Very Strong Association	Dose Response	Confounders Would Increase Effect	Final Level of Evidence Strength
He et al 2015,[49] Leversedge et al 2020,[50] Rbia et al 2019,[52] Means et al 2016[51] (RCT)*	Sensory recovery, 2PD	−2	0	0	0	−1	0	0	0	Very low(⊕○○○)
Leversedge et al 2020,[50] Rbia et al 2019,[52] Means et al 2016[51] (RCT)†	Meaningful recovery	−2	−1	0	0	−1	0	0	0	Very low(⊕○○○)
Means et al 2016 (RCT)‡	Postoperative function (DASH)	−1	−1	0	−1	−1	0	0	0	Very low(⊕○○○)

Certainty of the evidence assessed using methods of the GRADE (36): *High* (⊕⊕⊕⊕): Further research is very unlikely to change our confidence in the estimate of effect. *Moderate* (⊕⊕⊕○): Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. *Low* (⊕⊕○○): Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. *Very low* (⊕○○○): Any estimate of effect is very uncertain.

*Outcome measure: Sensory recovery, 2PD. A total of four studies including 323 individuals. One RCT and three comparative cohort studies. Three studies (287 individuals) showed better postoperative discriminative sensation after peripheral nerve reconstruction, whereas one study (37 individuals) showed no difference in sensory recovery compared with standard treatment. Deduction due to study design, there only being a small RCT and the rest comparative cohort studies with many individuals lost to follow-up and ROB.

†Outcome measure: Meaningful recovery. A total of three studies including 170 individuals. One RCT and two comparative cohort studies. One study (110 individuals) showed that allograft leads to better postoperative meaningful recovery than standard treatment. Two studies (60 individuals) showed no difference when compared with standard treatment. Deduction due to study design, there only being a small RCT and the rest comparative cohort studies with many individuals lost to follow-up, inconsistency, and ROB.

‡Outcome measure: Postoperative function (DASH). One study, an RCT including 23 patients.

It is not possible to assess whether PNA gives better self-reported postoperative function than other treatments for peripheral nerve surgery. Only one study was found, with a limited number of included individuals, many of whom were lost to follow-up, and deductions were, therefore, made on quality, inconsistency, and ROB.

Disabilities of the Arm Hand and Shoulder questionnaire (DASH), where no differences were seen between PNA and nerve conduit groups. Lans et al[53] showed that individuals operated on with neuroma excision alone have significantly worse self-reported function and pain than those treated with neuroma excision and reconstruction, where PNA was one of the methods used.

Means et al[51] also assessed pain postoperatively, according to the visual analogue scale, with no difference demonstrated between the PNA and nerve conduit groups.

Narrative Synthesis

The results for the outcome measures for postoperative function vary between the studies. No conclusion can be made since the assessment of this outcome has insufficient reliability and shows very low certainty of evidence (⊕○○○).

Outcome Measure 2: Adverse Events/Complications

Four studies, two of which are retrospective, reported adverse events. He et al[49] reported no complications directly linked to the use of the human acellular nerve graft (hANG). Only symptoms such as mild postoperative pain, redness, and a transient effect on blood tests were reported. Two patients underwent reoperation 6 months postoperatively due to a tendon adhesion, described as being related to the trauma itself.

Leversedge et al[50] assessed the proportion of patients with PNA compared with nerve conduits needing reoperation due to neuroma formation after surgery. No significant difference (3% versus 7%) was seen between PNA and nerve conduits. In addition, an infection described in the allograft group was concluded not to originate from the allograft. It is not further described how this conclusion was drawn. Two patients in the nerve conduit group and one patient in the allograft group reported increased postoperative pain. It was not described how this pain affected the patient's function or quality of life.

Means et al[51] reported no difference in rate of complications between study groups. A skin infection was seen in the PNA group, while the nerve conduit group reported two possible product-related complications: one patient with mild chronic pain, treated with anti-inflammatory drugs, and one patient with tube displacement as well as a fungal infection and osteomyelitis. This complication led to finger amputation; thus, it was considered very serious.

Rbia et al[52] showed no difference between the PNA and conduit group regarding complications. However, one individual had neuroma formation, and another developed allodynia followed by CRPS after reconstruction with PNA. This was considered a serious side effect of the treatment. In the nerve conduit group, a postoperative infection was seen but not specified in detail.

Narrative Synthesis

It is not possible to draw any conclusions for the outcome adverse events, as the complications are not reported systematically in any controlled study. The certainty of evidence for this outcome is regarded as very low (⊕○○○).

Outcome Measure 3: Effect Measure for Evaluation of Rehabilitation Potential

No articles were identified regarding the evaluation of rehabilitation potential; hence, no grading of certainty of the evidence is possible to perform.

Outcome Measure 4: Health-related Quality of Life

Means et al[51] presented self-reported function from the DASH questionnaire, where the patient assesses their own ability to perform various activities using the upper limb. DASH also includes measures of quality of life and activities of daily life. No differences were observed between the groups in self-reported function.

Narrative Synthesis

The available evidence for this outcome is regarded as very low, and it is not possible to assess how the PNA affects health-related quality of life compared with other interventions (⨁◯◯◯).

Outcome Measure 5: Health Economic Aspects

No articles were identified on the evaluation of the health economic aspects; hence, no grading of certainty of the evidence is possible to perform.

DISCUSSION

The use of a PNA has been proposed as a novel treatment for restoring function in peripheral nerve surgery as a complement to standard treatment when a defect is found between severed nerve ends.[31,54,55] Despite more than 8500 published articles, the benefits of the use of PNA remain unclear. The guidelines for implementing the use of PNA in peripheral nerve reconstruction or in surgical treatment for neuroma formation are missing. Lans et al[53] presented individuals to have worse pain and self-reported function if treated with neuroma excision alone compared with neuroma excision and reconstruction, where PNA was one of the methods. Results, although excluded in this review, presented by Rambau et al[23] support this, reporting that most patients with painful neuromas treated with PNA showed improved pain. Our systematic review, with an extensive literature search, shows a scarcity of high-quality controlled studies on the use of PNA. The decision that the surgeon must make when treating a nerve injury with a nerve defect may be difficult. Many factors need to be weighed before performing the reconstruction. These factors include the type of nerve, the location of the nerve injury, any delay in the reconstruction, the length of the nerve defect, the condition of the wound, the risk for wound infection, and available graft material.[56]

For all presented and reviewed outcome measures, there are no controlled studies with a low ROB. The few controlled studies that do exist have small patient cohorts, and are considered to have a high ROB due to deficiencies in study design, size, or lack of blinding, as well as with a risk of publication bias. Another important point is that in included studies with a control group, the groups are also heterogenous and not comparable with meta-analysis as described by Chung et al.[57]

Most studies included in the previously published reviews that fulfilled the criteria of the present project's PICO criteria did not include a control group and were, therefore, excluded from the analysis. Most of these studies, defined as uncontrolled, described PNA as a safe product, with a favorable outcome, and with some return of function after surgery. However, four identified noncontrolled case series reported negative results after surgery with PNA, where PNA surgery failed[36–39] reporting no functional recovery,[37,39] and reports on histological and immunohistochemical analysis indicated failure of the PNA with loss of physiological microvascular architecture.[38] With a substantial risk of publication bias, assuming that studies with positive results are published more easily than those with negative ones, it is difficult to comment on these studies. However, it is noteworthy that published studies show diverging results.

Another factor to consider is if it is suitable to include studies that compare PNA to nerve reconstruction with nerve autograft as well as reconstruction with nerve conduits. Three of the five included studies compared PNA with reconstruction with nerve conduits. The latter is a method established over 30 years ago and has been used to reconstruct limited nerve defects as an alternative to autologous graft for a substantially longer time than PNA. Several studies and well-conducted systematic reviews[28,58] indicate an acceptable outcome, which is why comparisons to various nerve conduits are warranted. The results of the outcome parameters for PNA, though compared with a conduit, do not change and can help to understand the meaningful recovery after such an intervention.[11,59–63]

Since it is not possible to draw any conclusions about whether the use of PNA is better or as good as reconstruction with a nerve autograft or with nerve conduits, one must consider the risk of potential serious side effects. As the side effects are not systematically described in the studies, it is, therefore, not possible to draw any conclusions. The possible side effects, such as pain, infection, and CRPS, have not been assessed based on severity or clinical significance in the presently included articles. The large numbers of patients lost to follow-up in the reviewed articles also entail a great deal of uncertainty about possible side effects not presented.

Most surgically treated nerve injuries affect digital nerves,[64] leading to impact on only sensory function, while fewer peripheral nerve injuries involve larger nerve trunks in the upper and lower extremities,[64] where recovery of muscle function also must be evaluated. Today, larger peripheral nerve injuries with a defect between the proximal and distal nerve ends are treated with autologous nerve grafts, usually using harvested sural nerves.[20] We do not know the potential use for PNA in larger peripheral nerve reconstruction, as the survival of motor nerve cells is believed to be greater than in sensory nerve cells after peripheral nerve injuries.[65] No studies have emerged regarding this topic in our review.

The methodology used in this review was structured, transparent, and internationally well accepted. Unlike other published reviews in the field, the present systematic review includes only studies that contain a control group

of patients. This markedly reduced the number of studies in the synthesis but gives strength to the evaluation of the use of PNA based on a scientific approach with less risk of systematic bias. A further strength of the current review is the neutral position of the expert group. This contrasts with many published studies that are sponsored by companies providing the products that are available.

In summary, the level of evidence for the use of PNA in peripheral nerve surgery, whether in nerve reconstruction or in the surgical treatment of neuroma formation, is not enough to draw any conclusions about the usefulness in current clinical practice.

CONCLUSIONS

The scientific basis for the use of PNA in peripheral nerve surgery, or in surgical treatment of neuroma formation, has insufficient reliability and shows very low certainty of evidence (⨁◯◯◯). The insufficient reliability of the scientific literature is due to small numbers of participants, noncomparable control groups, significant and unexplained loss to follow-up, low precision in data and in some cases, a risk of publication bias as well as low certainty of the evidence (⨁◯◯◯). Therefore, we conclude that with existing publications, it is difficult to assess the usefulness of PNA compared with reconstruction with a nerve autograft or a nerve conduit, regarding the functional outcome after surgery. Nor can we assess the proportion of postoperative complications in PNA treatment due to insufficient reliability of the scientific evidence. Properly conducted, RCT studies on the use of PNA in treatment of peripheral nerve injuries or surgical treatment of neuroma formation are required.

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DISCLOSURES

Dr. Chemnitz has participated in a course organized by Axogen Inc. Alachua, FL, without financial interest. Dr. Dahlin has lectured for Axogen Inc. Alachua, FL, on two occasions and received two products of nerve allograft for a small experimental research study. The other authors have no financial interest to declare.

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