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Advances of Peripheral Nerve Repair Techniques to Improve Hand Function: A Systematic Review of Literature

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Abstract: Concepts of neuronal damage and repair date back to ancient times. The research in this topic has been growing ever since and numerous nerve repair techniques have evolved throughout the years. Due to our greater understanding of nerve injuries and repair we now distinguish between central and peripheral nervous system. In this review, we have chosen to concentrate on peripheral nerve injuries and in particular those involving the hand. There are no reviews bringing together and summarizing the latest research evidence concerning the most up-to-date techniques used to improve hand function. Therefore, by identifying and evaluating all the published literature in this field, we have summarized all the available information about the advances in peripheral nerve techniques used to improve hand function. The most important ones are the use of resorbable poly[(R)-3-hydroxybutyrate] (PHB), epineural end-to-end suturing, graft repair, nerve transfer, side to side neurorrhaphy and end to side neurorrhaphy between median, radial and ulnar nerves, nerve transplant, nerve repair, external neurolysis and epineural sutures, adjacent neurotization without nerve suturing, Agee endoscopic operation, tourniquet induced anesthesia, toe transfer and meticulous intrinsic repair, free auto nerve grafting, use of distal based neurocutaneous flaps and tubulization. At the same time we found that the patient's age, tension of repair, time of repair, level of injury and scar formation following surgery affect the prognosis. Despite the thorough findings of this systematic review we suggest that further research in this field is needed.

Keywords: Advances of nerve technique, hand function, neural regeneration, nerve repair techniques, peripheral nerve injury, peripheral nerve repair.

INTRODUCTION

A Brief History

The understanding of peripheral nerve injuries dates back to the nineteenth century [1, 2]. World War I and World War II brought about invaluable experiences in terms of classification of nerve injuries and surgical interventions, at the same time, sieving out unreliable techniques and leading to the modern era of direct nerve repair [1]. However, concepts of neuronal damage and repair date back to ancient times. Wound closure and apposition of nerve ends was originally described by Paul of Aegina sometime during the 7thcentury [3]. Neuronal degeneration were discovered and explained in Augustus Waller's article in 1850s [4, 5]. In 1864 Nelaton described secondary nerve repair and primary epineurial nerve suturing was explained by Hueter (1871, 1873) [6]. Techniques used to optimize suturing and regeneration of nerves where described in early 1880s by Mikulicz (1882) and Loebke (1884) describing sutures and bone shortening to reduce nerve tension, respectively [7]. Nerve grafting was described by Albert in 1876 for the first time [7]. Refining of these techniques and further experiences came later from treating war injuries, as described earlier [1].

Nerve Injuries and Degeneration

Several different classification of nerve injuries exist. According to Seddon [8] nerve injuries can be referred to as neuropraxia, axonotmesis and neurotmesis according to the disruption of the internal structure and consequently in order of worsening prognosis. Neuropraxia is a reversible condition when the electrical signal fails to travel through a nerve segment, when there is no anatomical disruption in the affected neuron [9]. There is minor damage to the axon and hence the prognosis is good [8]. Axonotmesis is when there is complete interruption of the axon in the affected neuron [9]. Neurotmesis describes the complete derangement of axons and supporting connective tissue and has the worst prognosis in these three types of nerve injury described by Seddon [8]. Sunderland [10] classified nerve injuries into first, second, third, fourth and fifth degree nerve injury in order of severity of the injury. Lorei and Hershman [11] divide neural traumas into chronic injuries or entrapment neuropathies, caused by repetitive trauma or compression, and acute injuries, which is caused by direct trauma leading to immediate onset of symptoms. Distal degeneration of neurons following traumatic injury has been termed

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Wallerian degeneration since Waller [5] described posttraumatic changes in peripheral nerves in 1850. It is important to note that endoneurium, the Schwann sheath and blood vessels remain intact [12] despite the occurrence of wallerian degeneration. Proximal changes in the neuron, however, have been termed axonal degeneration [12].

Nerve Repair

The purpose of nerve repair is the precise apposition of the two sides of transected nerve using a minimum number of sutures while dissecting nerve ends just to the extent necessary to achieve appropriate alignment with minimal tension [12]. Best return of function is possible if and only if the motor and sensory parts of a nerve are accurately and correctly connected. Deutinger *et al.,* [13] clearly states that for reestablishing the sensory function a nerve, particularly in median nerve injuries, intra-operative sensory motor differentiation is helpful. Intraoperative motor-sensory differentiation is currently possible with electrophysiological, immunohistochemical, histochemical and anatomical methods [12].

Branching and fascicular formation are observed in peripheral nerves [12]. In 1945 Sunderland [14] observed branching of musculocutaneous nerve every few millimeters. Following this observation numerous surgeons become pessimistic about the probability of successful nerve grafting and intraneural dissection since the assumption was made that this pattern of branching occurs at every level in the arm and forearm [12]. Jabaley, Wallace and Heckler [15] in 1980 showed in their dissection of median, radial and ulnar nerves that there are no adjacent fibers branching off the main nerve trunks for a considerable distance. Despite there being connections, it does not make fascicular repair, intrafasciular grafting or intraneural neurolysis impossible [12]. Having sound knowledge of the internal neural anatomy regarding nerve repair has been emphasized by Williams and Jabaley [16] in1986.

Several methods can be applied to bridge a nerve gap. These include direct repair, neurotization, nerve transfer, nerve allografts, various tubes and conduits, grafting, and tissue expansion [12, 17, 18]. Nerve transfer can be explained as a procedure to reinnervate a motor or sensory area by transferring another nerve [12]. Neurotization is the direct placing into an end target muscle of a proximal motor nerve stump [12]. There are three types of nerve repair, nevertheless neither has proved to have a comparative advantage over the others [12]. Each of these techniques has some advantages and disadvantages.

Epineurial Repair

The conventional technique for suturing lacerated nerves is the so-called epineurial repair [12]. Daniel and Terzis [19] list several advantages of this technique which include short execution time, minimal magnification, technical ease, not invading the intraneural contents, being applicable to both primary and secondary neural repairs and the placement of sutures only in the outer investing sheath. Tension from natural retraction despite no loss of nerve tissue, compromising the accurate alignment of fascicles, sutured epineurium and cut axonal interphase being in the same plane, controversial outcome, the need for many sutures in order to achieve structural integrity of the repaired nerve rank among the most significant disadvantages [19].

Perineurial (Fascicular or Funicular) Repair

This technique was initially described by Langley and Hashimoto [20] in1917 and its superiority over epineurial repair is still questioned. This could be due to the controversial findings of researchers. Perineurial repair tends to be favoured over funicaular suture by Bora [21], Goto [22], Grabb *et al.,* [23], Wise *et al.,* [24] Yamamoto [25] and Brushart, Tarlov and Mesulam [26] while Sunderland [27] and Young, Wray and Weeks [28] find no difference between the two techniques.

Taking into account the morphological and neurophysiological aspects of fascicular nerve repair, it proves to be more beneficial in terms of stabilizing and neuronal pathways when the fibers are well localized at the nerve terminals [29]. The technique of choice for the majority of the acute nerve lacerations, however, is suturing the outer epineurium as it is a faster and simpler method which requires little disruption of the internal structure of the nerve, argues Orgel [30]. Jabaley [31] in the “Current concepts of nerve repair” explains the indications for perineural and epineural repair. He states that the technique is contraindicated in multifascicled nerves but is the treatment of choice in nerve grafting and in nerves with less than five fascicles [31]. According to Langley and Hashimoto [20] the advantages of funicular repair are better recovery of motor and sensory end-organs, greater regeneration of axons entering distal nerves, coaptation of perineurial tubes allowing for more desirable alignment of fascicles and better myelination of the stumps. Nonetheless, the drawbacks are described by Sunderland [27] as greater fibrosis at the site of suture, increased injury to vessels at the nerve ends, extended operative duration, possibility of compromising the vascular supply of isolated fasciculi, discontinuity of fasciculi on a one-to-one basis and the inability to approximate small funiculi. Furthermore, Madden and Peacock [32] point out to the possibility of precisely matching the ends of transected nerves by identifying sensory and motor fascicles in both distal and proximal stumps.

Group Fascicular Repair

Group fascicular repair is feasible if a nerve is lacerated where branches in the transected nerve are well formed and readily identifiable in the main trunk [12]. In this case, motor and sensory fascicles can be matched correctly and motor-sensory cross-innervation can be avoided. Nevertheless, this technique is currently not very practical due to the long operative process, despite the existence of numerous histochemical staining techniques aiding the differentiation between motor and sensory axons [33-35]. Indications for group fascicular repair at different levels in the upper limbs are reported by Jabaley [16, 31].

Nerve Grafting

Nerve grafting dates back to Philipeaux and Vulpian in 1817 [3]. During the early 1970s Millesi recommended nerve grafting for any nerve gap larger than 2 cm and achieved great results in ulnar, median and radial nerve lesions [36-40]. Some of his most significant techniques in interfascicular nerve grafting include: 1) Grafts to bridge the gap should be cut slightly longer than the lesion itself 2) connective tissue between groups of fascicles should be dissected rather than every individual fascicle. 3) preserve only the healthy tissue and if in doubt, resect 4) dissection of fascicles should be both at the distal and proximal ends in relation to the lesion in a normal tissue. 5) In matching the stumps a drawing of the cut surface can prove helpful.6) five to 6 autografts are needed for the median nerve and four to five for ulnar and radial nerves [40].

Nerve Transfer

Another method to bridge a nerve gap is by nerve transfer. This is similar to that of tendon transfer [12]. In this procedure spare motor units are surgically re-organized in order to reestablish a vital missing function and have the potential to restore sensibility [12]. Nerve transfer is done to convert a high-nerve injury to a low nerve injury, avoid nerve grafting and to preserve muscle structure [12].

Purpose of Our Review

There is not sufficient information about the advances in repairing peripheral nerves and how these can be beneficial in terms of improving hand function. Therefore, finding the correct indications for applying different nerve repair techniques can be a challenge. There are no articles bringing together and summarizing the advances in peripheral nerve techniques. The purpose of this study is to summarize all the available information regarding the advances in peripheral nerve techniques which help to improve hand function by identifying and evaluating all the published literature in this field. The studies reporting different surgical methods and management of peripheral nerve injuries were searched mainly using PubMed, Medline, EMBASE, CINAHL (EBSCO), ZETOC, and AMED. This systematic review is intended to provide a good basis for identification and selection of peripheral nerve repair techniques which have proven to be helpful in improving hand function.

MATERIALS AND METHOD

The studies referencing different nerve repair techniques were searched using the electronic databases Medline, CINAHL (EBSCO), ZETOC, PubMed, EMBASE, AMED, PREMEDLINE In-Process & Non-Indexed Citations (OvidSP), ASSIA (CSA Illumina), Conference Proceedings Citation Index: Science (ISI) on Web of Knowledge, PsycINFO (OvidSP), Science Citation Index (ISI) on Web of Knowledge, Social Sciences Citation Index (ISI) on Web of Knowledge and Cochrane Library (Wiley). To cite relevant articles the following keywords were used: peripheral nerve injury, peripheral nerve repair, neural regeneration, hand function, nerve repair techniques. The inclusion criteria were based on 1)Identification of nerve repair techniques 2)describing nerve injuries and regeneration 3)nerves of the forearm and hand 4)commented on improvement or deterioration of hand function. Studies were excluded which 1) did not comment on nerve repair techniques of any kind 2) did not involve peripheral nerves 3) identified nerve repair techniques only applicable to non-human species 4) did not involve the hand 5)were not available for free viewing. A total of 187 articles were reviewed. 24 articles were identified as relevant according to the inclusion criteria. These studies were summarized and the relevant information is presented in this review.

RESULTS

Out of 187articles reviewed, 24 studies were identified as relevant according to the inclusion criteria. Subsequently, these were reviewed carefully and the results summarized in Table **1**. Aberg *et al.,* [41] compare the effectiveness of resorbable poly[(R)-3-hydroxybutyrate] (PHB) against epineural end-to-end suturing for nerve injuries at wrist/forearm. The overall conclusion of this study is that PHB is a safe alternative for end-to-end suturing, however it is important to note that most methods applied reported no statistically significant difference between the treatment and control groups [41]. Furthermore there was great variability observed for the evaluating techniques [41]. Cherqui *et al.,* [42] evaluate the surgical treatment of lipofibrohamartoma of the median nerve and state that graft repair following resection of the tumour may be the best treatment [42]. They report that the outcome may be even better for pediatric patients [42]. Ducic *et al.,* [43] transferred the radial sensory nerve to the ulnar digital nerve of the thumb and the radial digital nerve of the index finger in 2 case reports of patients with proximal median nerve injury [43]. In this radial sensory neurotization of the thumb and index finger they report faster return of sensation with digital nerve transfers of the dorsal radial sensory nerves compared with conventional median nerve repairs [43]. Yuksel *et al.,* [44] report on two extreme cases of peripheral nerve injuries with no chance for direct repair. A side-to-side neurorrhaphy between the median and ulnar nerves, and an end-to-side neurorrhaphy between the median, radial and ulnar nerves was performed. In this report, the two surgical procedures, referred to as alternative nerve repair techniques by Yuksel *et al.,* [44], are considered to be reasonable treatments for challenging peripheral nerve lesions after both patients regained their protective sensation and returned to work. A study by Lenz-Scharf *et al.,* [45] involving 17 children with upper extremity nerve lesions showed results after nerve transplantation within a timeframe of six weeks. The subjects were treated with sural nerve transplant to median or ulnar nerves and observed for 2.9 years on average [45]. Lenz-Scharf *et al.,* [45] reported good to excellent results. They argue that nerve regeneration at the proximal end of the lesion is best within 6 weeks as Wallerian degeneration is complete and nerve grafting should be done within this period [45]. However, it is important to note that complete restoration of muscle motor units did not occur in the examined cases [45].

Battiston and Lanzetta [46] present the clinical outcome of 7 patients with ulnar nerve lesion at the elbow in which a distal connection was made between anterior interosseous nerve and the superficial sensory palmar branch of the median nerve with the motor and sensory components of the ulnar nerve at Guyon's canal. The patients were followed up from 1 to 3.5 years and the results were graded using the Highet-Zachary scale [46]. In all but one of the cases good sensory and motor recovery was observed. Only one of the cases did not achieve good motor recovery, however protective sensation returned in this subject [46]. Wang, Zhu and Zhang [47] explain the clinical applications and anatomical basis for the repair of thenar branch of the median nerve and deep branch of ulnar nerve by transferring the pronator quadratus branch of anterior interosseous nerve. This technique was used in 20 ulnar nerve injuries and 17 of these were followed up from 2 to 7 years. The muscle strength returned in different degrees ranging from M2 to M5 [47]. Barrios and de Pablos [48] review the results of surgically treated ulnar, median and radial nerve injuries in 33 children.18 patients were treated with interfascicular grafting, 14 with decompressive external neurolysis and 5 with epineural sutures [48]. In 84% of the children useful sensory function was restored and 67% regained satisfactory motor function [48]. Interestingly, the median nerve showed the best ability for recovery in terms of motor and sensory function regardless of the type of injury [48]. At the same time, radial nerve proved to have a worse prognosis in terms of regaining motor function in lesions affecting the continuity of the nerve trunk [48]. Barrios and de Pablos state that the worsening prognosis was related to a time period of longer than 1 year from nerve damage to surgery [48].

Faivre *et al.,* [49] review the functional results following distal replantation without nerve suturing in a cohort of 8 children. All children regained discriminatory sensation through the adjacent and spontaneous neurotization after distal digital replantation [49]. Thus they report that children are excellent candidates for replantation of distal extremities even without nerve suturing [49]. Schäfer *et al.,* [50]. Compare the open surgical epineural neurolysis of the median nerve in carpal tunnel syndrome with agee endoscopic operation and report that the endoscopic group were able to return to work significantly earlier and had reduced postoperative pain compared to the surgical group. They conclude that the epineural neurolysis is not necessary [50]. Bjorkman *et al.,* [51] investigate the improvement of hand function following tourniquet induced anaesthesia after deafferentation.

Table **1** demonstrates the studies reviewed in this systematic review. The authors, type of study, number of patients involved, techniques and outcome of the studies have been summarized.

Interestingly they report that this resulted in significant and rapid improvement in tactile discrimination, grip strength and sensibility of the contralateral hand [51]. Thus they conclude that this technique may have potential clinical application [51]. Vilkki [52] reports significant improvement of hand function in congenitally adactylous hand after microsurgical 3-jointed second toe transfer and meticulous intrinsic repair. Abundant nerve supply was found to be important in normal growth of the transferred nerve [52]. 14 out of the 17 patients regained the ability to pinch [52]. Sanmartin *et al.,* [53]. Review the results of 105 cases of ring avulsion injuries and conclude that good sensory recovery is not achieved by primary neuronal repair in most cases.

Free auto nerve grafting in median and ulnar nerve repair had no obvious effects in long-term improvement of the hand function following severe electrical injury of the wrist [54]. In this study Xu, Li and Chen [54] report that the 2 out of the 47 cases repaired by compound tissue grafting of sural nerve and deep facia carried by small saphenous veins demonstrated uncertain results. However, 3 cases of proximal neuronal anastomosis showed fairly good results. They conclude 2 factors to be responsible for the poor outcome following nerve grafting: scar formation and inadequate blood supply [54].

Haase and Chung [55] investigate the primary repair of 2 cases of high ulnar nerve injuries and report a consistent poor outcome due to the distance between the innervated muscles and the site of injury. In these procedures the distal branch of anterior interosseous nerve was transferred to the distal motor branch of the ulnar nerve which was reported to be a much better method than the conventional primary neurorrhaphy for this type of injuries [55]. Song *et al.,* [56]. Valuate the application of distal based neurocutaneous flaps in repair of hand wounds. This simple procedure is less invasive, has a high survival rate and results in sensory function recovery of the hand [56]. They also report recovery in hand function and two point discrimination after cutaneous nerve ending anastomosis [56].

Rosen *et al.,* [57] assess the functional outcome of median and ulnar nerve repair in a study of 19 patients and report that there was no significant improvement in two point discrimination over time. However, they suggest the use of alternative or complementary test instruments for measuring the tactile gnosis [57]. Furthermore, most changes occurred during the first year and later it was mainly the motor function that improved [57]. Stevanovic *et al.,* [58] use nerve grafts to bridge gaps in avulsion injuries of the thumb. They state that the cold ischaemia time and patient's age had no significant effect on the function or survival of the transplanted thumb [58]. However, the grip strength was always less than normal and key pinch was 60% of normal [58]. Moreover, when a venous backflow was established and continued for at least 20 minutes the transplanted thumb always survived without complications [58].

Goldberg *et al.,* [59] determine the number of suture strands crossing the repair site in a cadaver as the most significant variable that would influence the nerve repair strength. Braga-Silva *et al.,* [60] investigate the effect on recovery of late tubular repair of human median and ulnar nerves using a silicon tube filled with autologous bone marrow mononuclear cells from iliac crest aspiration. The effects of pain as well as the motor and sensory recovery were assessed after 1 year and the tube filled with mononuclear cells showed better recovery than the empty tubes [60]. Hence they claim this method to be better in term of neuronal regeneration when using conventional tubular reconnection [60]. Mondelli *et al.,* [61]. Review the results of surgical decompression of carpal tunnel syndrome and report that elderly patients showed less improvement in all modalities compared to the 20-54 year group, probably due to lower repair capacity and greater preoperative damage. Deutinger *et al.,* [62]. Report better sensibility recovery after motor-sensory differentiation in median and ulnar nerve repair. Lohmeyer *et al.,* [63] repaired 15 digital nerve lesions in 14 patients using interpositional grafting of a hollow collagen I conduit and state that this tubulization technique to be an alternative to autologous nerve grafting since it successfully bridges short nerve gaps. In a review of treatment possibilities of thumb avulsion injuries Pfeiffer [64] recommends direct nerve repair over use of nerve-grafting in order to prevent neuroma formation.

Table 1. Summary of the Relevant Studies

Study/Year	Type of Study	Number of Patients	Follow Up Period	Number of Patients	Method/Technique	Outcome
Aberg *et al.*/2009 [41]	a prospective, assessor-blinded, randomised clinical study	12	18 months	12	Resorbable poly[(R)-3-hydroxybutyrate] (PHB) and epineural end-to-end suturing.	PHB is a safe alternative for end-to-end suturing
Cherqui *et al.*/2009 [42]	Case report	1	1 year	1	Tumour resection and graft repair of median nerve:	Maybe the best surgical treatment of lipofibrohamartoma.
Ducic *et al.*/2006 [43]	Case report	2	14 months	2	Radial nerve transfer in patients with proximal median nerve injury.	Faster return of sensation with digital nerve transfers of the dorsal radial sensory nerves compared with conventional median nerve repairs.
Yuksel *et al.*/2004 [44]	Case report	2	9 and 14 months	2	Side to side neurorrhaphy and end to side neurorrhaphy between median, radial and ulnar nerves.	Patients regained their protective sensation and returned to work.
Lenz-Scharf *et al.*/2004 [45]	Longitudinal observational study	17	2.9 years	17	Sural nerve transplant to median or ulnar nerves.	Good to excellent results, but it is important to note that complete restoration of muscle motor units did not occur in the examined cases
Battiston and Lanzetta/1999 [46]	Longitudinal observational study	7	1 - 3.5 years	7	Connection was made between anterior interosseous nerve and the superficial sensory palmar branch of the median nerve with the motor and sensory components of the ulnar nerve at Guyon's canal.	Good sensory and motor recovery was observed in all but one of the cases.
Wang Y. Zhu S. Zhang B./1997 [47]	Longitudinal observational study	20	2 – 7 years	20	Median and ulnar nerve repair by transferring the pronator quadratus branch of anterior interosseous nerve.	The muscle strength returned in different degrees ranging from M2 to M5.
Barrios and de Pablos/1991 [48]	15-year retrospective study	33	2 years	33	Interfascicular grafting, decompressive external neurolysis and epineural sutures.	Majority regained satisfactory sensory and motor function.
Faivre *et al.*/2003 [49]	Longitudinal observational study	8	8 years	8	Adjacent and spontaneous neurotization after distal digital replantation without nerve suturing.	Children are excellent candidates for replantation of distal extremities.
Schafer *et al.*/1996 [50]	prospective randomised study,	101	9 months	101	Epineural neurolysis versus Agee endoscopic operation:	Epineural neurolysis is not necessary, because when Agee endoscopic operation is performed the results are better.
Bjorkman *et al.*/2004 [51]	Prospective clinical study	20	25min before – 60 min after anaesthesia	20	Tourniquet induced anesthesia after deafferentation	Rapid improvement in tactile discrimination, grip strength and sensibility of the contralateral hand
Study/year	Type of study	Number of patients	Follow up period	Number of patients	Method/Technique	Outcome
Vilkki/1995 [52]	Longitudinal observational study	18 microsurgical toe transfers	1.5 – 6 years	18 microsurgical toe transfers	Microsurgical 3-jointed second toe transfer and meticulous intrinsic repair:	Most patients regained ability to pinch
Sanmartin *et al.*/2004 [53]	retrospective cohort study	105	139 days (mean)	105	Review results of 105 cases of ring avulsion injuries and Primary nerve repair.	Good sensory recovery is not achieved by primary neuronal repair in most cases
Xu, J *et al.*/2000 [54]	Prospective study	47		47	Free auto nerve grafting in median and ulnar nerve repair.	Had no obvious effects in long-term improvement of the hand function. scar formation and inadequate blood supply responsible for poor outcome following nerve grafting

(Table 1) contd…..

Study/Year	Type of Study	Number of Patients	Follow Up Period	Number of Patients	Method/Technique	Outcome
Haase and Chung/2002 [55]	Case report	2	6 months and 1 year	22	Primary nerve repair by nerve transfer	For these types of injuries, this method is better than the conventional primary neurorrhaphy.
Song *et al.*/2009 [56]	Longitudinal observational study	187	2 months – 3 years	187	Distal based neurocutaneous flaps	Less invasive and results in sensory recovery, two point discrimination and improvement in hand function after cutaneous nerve ending anastomosis.
Rosen *et al./2000* [57]	Longitudinal cohort	19	4 years	19	Median and ulnar nerve repair	No significant improvement in two point discrimination
Stevanovic *et al.*/1991 [58]		17 thumbs		17 thumbs	Nerve grafting in avulsion injuries	Both key pinch and grip strength were less than normal.
Goldberg *et al./2007* [59]		67 digital nerves	Not applicable	67 digital nerves	Digital nerve repair	Number of suture strands crossing the repair site determine the nerve repair strength.
Braga-Silva *et al.*/2008 [60]	non-randomised retrospective study	44	1 year	44	Use of bone marrow mononuclear cells in addition to Tube-reconnection (tubular repair of median and ulnar nerves)	Better recovery in patients with filled tubes was observed.
Mondelli *et al.*/2004 [61]	3 year prospective study	282	6 months	282	Review the results of surgical decompression of carpal tunnel syndrome.	Elderly patients showed less improvement in all modalities
Deutinger *et al.*/1993 [62]	Longitudinal observational study	22	1 – 11 years	22	Motor-sensory differentiation in ulnar and median nerve repair	Better sensibility recovery.
Lohmeyer *et al.*/2009 [63]	a prospective cohort study and literature review	14	12 months	14	Tubulization: Interpositional grafting of a hollow collagen I conduit.	This is an alternative method to autologous nerve grafting.
Pfeiffer/1993 [64]					Direct nerve repair *vs* nerve-grafting	Direct nerve repair should be used in avulsion injuries of the thumb to prevent neuroma formation. Nerve-grafting is not recommended

DISCUSSION

In this systematic review we looked at various nerve repair techniques currently used for different types of nerve injuries to improve hand function. These include the use of resorbable poly[(R)-3-hydroxybutyrate] (PHB) [41], epineural end-to-end suturing [41], graft repair [42, 48, 58, 64], nerve transfer [43-55], side to side neurorrhaphy and end to side neurorrhaphy between median, radial and ulnar nerves [44], nerve transplant [45], nerve repair [47, 53, 57, 59, 62, 64], external neurolysis and epineural sutures [48], adjacent neurotization without nerve suturing [49], Agee endoscopic operation [50], tourniquet induced anesthesia [51], toe transfer and meticulous intrinsic repair [52], free auto nerve grafting [54], use of distal based neurocutaneous flaps [56] and tubulization [60-63].

There are, however, a number of factors that influence the functional outcome and recovery. Sunderland [10] argues that if enough axons can be directed to their end-organs and if the muscle is maintained in good condition through therapy then the affected muscle, even after a year of denervation, is able to regain almost 100% function. Therefore, functional deficits observed in muscles are due to a lack of adequate re-innervated muscle fibers, fiber mixing or persisting trans-synaptic neuronal changes which prevent the normal activity pattern [65].

Patient's Age

In peripheral nerve repair the functional results are inversely proportional to the patients age, holding all other variables constant [12]. For patients up to 20 years of age the regained two point discrimination value calculated in millimeters for ulnar and median nerve repairs has been found to be the same as the patient's age [66]. Onne [66] noted that in this type of nerve repair there was variable but generally poor recovery for patients between 20 and 31 and for those above 31 poor results were recorded. Digital nerve repairs, on the other hand, showed good functional recovery up to the age of 50 years [66]. Young, Wray, and Weeks [28] reported that patients older than 40 achieved no two point discrimination but protective sensation after digital nerve repairs. However, they reported useful two point discrimination in 80% of patients below 20 years of age [28]. Lundborg and Rosén [67] found that patients under 10 showed best results in term of regaining sensibility following transected median or ulnar nerves at the wrist level. Moreover, they observed a marked decline in recovery up to the age of 18 and a plateau thereafter [67]. Cherqui *et al.,* [42] argue that the result of nerve graft after tumour resection in lipofibrohamartoma of the median nerve may be better in pediatric patients. Mondelli *et al.,* [61] also report that elderly patients showed less recovery than the 20-54 year group. They argue that this might be due to lower repair capacity and greater preoperative damage [61]. Faivre *et al.,* [49] state that children are excellent candidates for replantation of distal extremities even without nerve suturing. Contradicting outcomes have been reported by Sunderland [10], who claims that there is no correlation between the patient's age and functional outcome. Venkatramani *et al.,* [68] support this statement and suggest that the patient's age should not be a criterion for denying treating and good results are expected if the procedure is done within 6 months.

Time of Repair

There is some degree of disagreement concerning the optimal timing for suturing transected nerves. Sunderland [10] and Ducker [69] recommend nerve repair within the first 10 days of injury whereas Kleinert and Griffin [70] and Holmes and Young [71] believe that the nerve repair should be at the time of maximal axoplasmic synthesis. Cabaud *et al.,* [72] support early treatment to minimize scarring in endoneurial space and benefit from early axonal sprouting. Seddon [8], however, states that fibrosis at 3 weeks offers a mechanical advantage for nerve suturing. Lenz-Scharf *et al.,* [45] argue that nerve regeneration is best within 6 weeks at the proximal end of the lesion as Wallerian degeneration is complete. Barrios and de Pablos state that the worsening prognosis was related to a time period of longer than 1 year from nerve damage to surgery [48]. Rosen *et al.,* [57] report that most functional recovery occurred within the first year of median and ulnar nerve repair and later it was mainly the motor function that improved.

Other Factors

The level at which the injury has occurred can also affect the outcome. The more proximal the injury, the worse the prognosis in terms of motor and sensory return [10, 73]. Moreover, more complete and rapid regain of function occurs in more proximally innervated muscles [12]. Another factor affecting the outcome is the tension of the repair. While the elasticity of the nerve tissue can prove helpful in bridging nerve gaps, Millesi [36] argues that human nervous tissue has an elongation capacity of 20% beyond which the conductivity is compromised. Xu, Li and Chen [54] assume 2 factors to be responsible for the poor outcome following nerve grafting: scar formation and inadequate blood supply.

Barrios and de Pablos [48] found that the median nerve had the best recovery but the radial nerve had the worst prognosis in term of motor recovery in lesions affecting the continuity of the nerve trunk. Sanmartin *et al.,* [53] conclude that good sensory recovery is not achieved by primary neuronal repair in most cases in a review of 105 ring avulsion injuries. Similarly, Haase and Chung [55] report consistently poor outcome in primary repair of 2 cases of high ulnar nerve injuries. Rosen *et al.,* [57] also report was no significant improvement in two point discrimination over time in 19 patients with ulnar and median nerve repair. Goldberg *et al.,* [59] determine the number of suture strands crossing the repair site in a cadaver as the most significant variable that would influence the nerve repair strength.

CONCLUSION

In this systematic review we have summarized the advances in nerve repair techniques which have been used to improve hand function. The most important ones are the use of resorbable poly[(R)-3-hydroxybutyrate] (PHB)[41], epineural end-to-end suturing [41], graft repair [42, 48, 58, 64], nerve transfer [43, 55], side to side neurorrhaphy and end to side neurorrhaphy between median, radial and ulnar nerves [44], nerve transplant [45], nerve repair [47, 53, 57, 59, 62, 64], external neurolysis and epineural sutures [48], adjacent neurotization without nerve suturing [49], Agee endoscopic operation [50], tourniquet induced anesthesia [51], toe transfer and meticulous intrinsic repair [52], free auto nerve grafting [54], use of distal based neurocutaneous flaps [56] and tubulization [60, 63]. The results have been summarized in Table **1**. We also identified factors that may affect the prognosis following surgery. Among the most significant are patient's age [10, 12, 28, 42, 49, 61, 66-68], time of repair [8, 10, 45, 48, 57, 69-72], level of injury [10, 12, 73], tension of repair [44], and scar formation following surgery [54]. Despite the thorough findings of this systematic review, we suggest that further research in this field is needed.

ACKNOWLEDGEMENT

None declared.

CONFLICT OF INTEREST

None declared.

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Received: October 14, 2011 Revised: October 22, 2011 Accepted: October 27, 2011