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Review Article

Outcome of human peripheral nerve repair interventions using conduits: a systematic review

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ABSTRACT

Background & objective: Peripheral nerve injury is very common, but repair is a challenging medical problem. Advances in medical sciences and technologies have however made tremendous breakthroughs in understanding repair mechanisms in nerve injury making this a fascinating area in neurotherapeutics. However, a systematic analysis of existing data is lacking, the present study was attempted to review existing literature in nerve repair studies in human beings and analyse outcome systematically.
Methods: A detailed search was made from various databases published in the last 10 years. The studies were included based on availability of data on the age of the patients, type of injuries, type of intervention and also on the minimal follow up period. Studies satisfying these criteria were subjected to a homogeneity test. On 263 patients from 3 homogeneous studies outcome parameters such as the functional improvement, sensory and motor recovery parameters were analysed.
Results: Results showed that conduits were safe and significantly more effective compared to the conventional sutures in effecting repair of sensory nerve injuries (Odds ratio 3.78; $P < .00001$).
Conclusion: In conclusion, repair of human sensory peripheral nerve using conduits is safe and more effective than direct nerve suture.

1. Introduction

As peripheral nerves are distributed superficially throughout the body, they are susceptible to injuries [1,2]. Road traffic accidents are the most common cause, most frequently affecting young to middle aged men. Symptoms of peripheral nerve injuries (PNIs) can vary, depending upon the location and type of the nerves affected. Among the PNIs, commonly injured nerves and nerve bundles in the upper limbs are the ulnar, median and radial nerves as well as the other branches of brachial plexus, while in the lower limbs, the sciatic and deep fibular nerves are more commonly involved. These injuries often result in marked functional impairment [3–5]. Although the peripheral nerve injuries typically do not threaten the life of the patient, they cause heavy societal burden by rendering hitherto healthy individuals physically and socio-economically handicapped, owing to their impact on day-to-day activities. The key to successful management of these injuries lays in proper clinical evaluation, supplemented with electrodiagnostic studies, preoperative imaging studies and careful management of adjoining soft tissue and bony injuries including surgical plans [5].

Nerve injuries range from the simple nerve compression or incision or severe nerve lacerations. The injured nerve is usually treated by techniques such as conventional direct end-to-end sutures, nerve grafts, conduits and neurorrhaphy [6]. When these direct repair techniques fail, nerve or nerve-muscle transplantation or other sophisticated nerobionics applications using man-machine interphases are also being tried but these techniques are costly, cumbersome and the latter still in early experimental stages. Though surgical suturing is the gold standard for treating nerve injuries with small gaps, repair of larger gaps is a major problem in peripheral nerve injury [7]. Regeneration of axons are often slow, non-uniform and directionless, and therefore fail to establish anatomical contact, continuity and connectivity with the result that functional recovery without technical aids is limited. Complications from operative procedures such as damage to blood vessels supplying nerves, operative trauma to graft nerves, local infections and immune rejection of nerve grafts [8] can also limit the full functional recovery. Various detrimental outcomes can result from absence of or partial recovery of nerve injury and include loss of sensations, chronic pain, dysaesthesias, motor paralysis, permanent disability, contractures

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and deformities [9]. However, as with other fields of medical science, management of nerve injury too received a boost in last two decades by various advances in the field of regenerative medicine.

Experimental validity for nerve graftings have been reported in dogs [10], rabbits and guinea pigs [11]. Reports on the use of nerve autografts in human are also available, though functional recovery was rarely reported in early studies. Types of human grafts used included single, cable, trunk and interfascicular [12]. They can be allografts or xenografts. Currently available nerve implants in the markets include peripheral nerve allografts, porcine materials based implants and biomaterial peripheral nerve scaffolds [9].

Nerve allograft is a decellularised and sterile extracellular matrix (ECM) obtained from human peripheral nerve tissue where the patient's own cells are incorporated into the ECM to remodel and form a tissue similar to the nerve epineurium [9]. One of the early biomaterials used as nerve scaffold was collagen. Collagen procured from human placenta and bovine dermis when administered in the form of injectable material, was reported to have the advantages of controlling fluid loss, maintaining the thermoregulatory status and preventing microbial contamination in human wounds. Collagen allografts were found reported to be useful as vascular and peripheral nerve prostheses useful to promote regeneration [13]. Collagen, an abundantly found structural protein in animals is the most prevalent component of the ECM and is now the most popular natural polymer in the manufacture of tissue engineered scaffolds [9]. Silicone (earliest synthetic) polytetrafluoroethylene (PTFE) are also deemed natural [14]. These materials being natural, have advantages like good cytocompatibility and biodegradability and therefore do not require surgical removal. However, silicone devices were not successful clinically because of the irritation caused to the patients [7]. PTFE also failed to mark success in the market.

Various biomaterials have been utilized to facilitate repair of nerve injuries. By definition a biomaterial is any material that comprises whole or part of a living structure or a biomedical device which performs, augments, or replaces a natural bodily function to improve the quality of life of the patients [15]. In nerve repair, their use is aimed at meeting the requisites necessary to accelerate nerve repairing process to improve functional outcomes [8]. Biomimetic nerve implants which provide ideal morphological, chemical and biological cues for functional recovery have been considered as exciting possibilities [9]. They include novel tissue-engineered scaffolds designed to bridge the nerve gap [16]. Currently nerve implants or scaffolds are available in two forms: conduits and wraps. Scaffold biomaterials can be hydrogels which are synthetic materials having properties similar to native tissue or natural materials which were bioactive. Scaffolds gave a distinct space for the development of nerve tissue, imparted mechanical stability and adhesion for recruited cells. In addition, Scaffolds can also serve as vehicles for delivery of drugs, genes, local tissue factors and for cell transplantation.

The major advantage of the neural conduits is that, it is a synthetic material and does not require a donor tissue from other parts of the body. Fortunately, none of the study has found any toxic reaction, especially in immunogenic reactions of conduits yet, therefore it is safer than conventional nerve graft method. Many studies have explored the efficacy of artificial nerve conduits in peripheral nerve regeneration and functional improvement in both animal models and humans, but there is no concrete conclusion on the efficacy of nerve conduits in neither neural regeneration nor sensory improvement. Lundborg et al. in a small randomized study in 1997 showed that tubular repair of peripheral nerve injury is not superior to conventional end to end nerve repairs [17]. Nevertheless, Bertleff et al. in 2005 demonstrated that though there were more complications in the experimental group, none of them was directly device related and the recovery of sensibility in the nerve guide group was at least as good as in the control group [18]. Most available studies on nerve repair prognosis are uncontrolled [18–27]. In a non-randomized retrospective study, Wangensteen et al. found conduits are safe and efficacious in 45% cases. Klein et al. in 2016, in uncontrolled studies reported use of nerve conduits in patients with large-diameter nerve lacerations, with results that time of treatment more important than age at the time of nerve repair. He noted the lack of motor recovery and attributed it to misdirected regrowing axons and the degeneration of motor endplates. While some further studies show an equivalent efficacy of sensory improvement compared to the conventional nerve autograft or end to end suture method [20–22,28–30], others have shown significant improvement over the conventional methods [31–33]. Subsequently, there is a debate on the efficacy and advantage of conduits compared to the conventional methods.

Thus it is evident that despite preclinical data showing promising effect of conduits in functional recovery of the peripheral nerve, there is debate on the clinical efficacy of conduits in human. Currently available human studies are plagued by deficiencies like small sample size, poor definition of inclusion and exclusion criteria, lack of clarity on uniformity of interventions performed, poverty of predefined outcome parameters and ambiguities about follow up period. Therefore the present study was undertaken to systematically analyse the effect of interventions by nerve conduits in functional recovery of peripheral nerve injuries in humans.

2. Method

2.1. Literature search

A detailed search was made from PubMed, EMBASE, Scopus, Cochrane library, CINAHL, PEDro databases and also on thesis publications from Indian Universities through the Shodhganga database (a nation-wide depository of academic dissertation works done in India stored as part of National knowledge network) and the Open thesis and conference proceedings from ProQuest database. The searches included “Peripheral Nerve Injury”, “Traumatic nerve injury”, “Nerve Injury repair”, “Peripheral nerve repair” AND “human” and subsequently filtered with “RCT”. Singular and plural forms of each term and regional variations in spelling were allowed. Studies were categorized based on the age of the patients, type of injuries, type of intervention, outcome parameters assessed and also the minimal follow up period. The quality of included studies was assessed using criteria recommended by the Cochrane Handbook for Systematic Reviews of Interventions and the data were extracted by two reviewers independently. Studies satisfying these criteria were segregated and were subjected to a homogeneity test. Those without acceptable homogeneity were excluded. Remaining studies were subjected to a meta-analysis. Outcome parameters such as the functional improvement and sensory and motor recovery parameters were analysed. Meta-analysis was conducted by an appropriate software (Revman, Cochrane community, Copenhagen).

2.2. Eligibility criteria

Studies were included in the current meta-analysis only if they met the following criteria: Prospective randomized controlled trials, robust design and execution, robust selection criteria for participants and controls, well-defined outcome parameters, blinded outcome assessment, and documented original quantitative research, was not a case study (sample size ≥ 2), and provided data in a format (e.g., number of cases and controls, exact number of sample events, mean and SD or exact values of statistical tests) that permitted the calculation of odds ratio and heterogeneity analysis in Rev. Man 5.1 software.

2.3. Data extraction

First and second authors (SKN & MA) had independently extracted the desired data from the included studies. Data included type of study, number of cases/controls, mean age, sex ratio, interval between injury and surgery, type of sutures, conduits, and intervention performed, mean duration of f/u, and outcome parameters. Other functional outcomes of significance were also extracted.

3. Results

3.1. Description of the included studies

Total 91 studies were reviewed for the analysis, out of which 85 records were identified through database search and 6 additional records identified through other sources such as conference proceedings, unpublished dissertation theses.

Of 91 records, 80 records were selected further for the review; remaining 11 records were excluded because of irrelevance. Among the 80 relevant records, 45 records were found to have non-availability of inclusion criteria or intervention details or follow up time or outcome measures. Remaining 35 homogenous records only included in the study. From the 35 selected studies 22 studies were further excluded because of the lack of clear definition of inclusion criteria (6 studies), lack of defined primary outcome parameters (8 studies), lack of clarity on type and timing of repair intervention (4 studies) and timing of assessment (4 studies). Out of the remaining 13 studies, 10 were excluded for lack of control group (7) or randomization (1) or blinding (2). Finally 3 studies with all relevant and unambiguous information and homogeneity of data were included for the quantitative analysis (Fig. 1).

3.2. Analysis of three randomized control trials in peripheral nerve repair

Three randomized trials were finally selected for the meta-analysis and the efficacy of conduits was compared with conventional sutures. There were a total of 223 male and 40 females in the studies. The weighted Odd's ratio for male gender between the conduits and sutures group was 1.63 and the three study series had no significant heterogeneity between them for the sex ratio between the two study groups ($P = .35$). The mean age was 35 ± 2 and 32 ± 6 years in the test and control groups respectively. The common site of injury was hand especially, finger, thumb, median and or ulnar nerve and limb and the most common mechanism of injury were reported as sharp cut, knife and crush (Table 1). The primary outcome for all the trials were static 2-point discrimination (s2PD) measured by a touch-test for two point discrimination and Semmes-Weinstein (SW) monofilament test by touch-test sensory evaluators. Follow-up period for assessing the efficacy of conduits in sensory recovery was regularly monitored in the trials and it was in the range of 2 weeks to 18 months post-surgery (Table 1).

Patients were mainly recruited based on the type and severity of the injury and only those who had nerve defects from injury were recruited in the trials. The main secondary outcome in the Berg2009 study was motor recovery, whereas other authors did not disclose with clarity on any secondary outcomes. Results from He2013 and Weber2000 studies found conduits to be safe and effective for the repair of nerve defects and also significantly better in improving the sensitivity (sensory outcome) compared to the conventional sutures. However Berg2009 study did not find significant difference between the conduits and sutures treated groups of patients (Table 1).

3.3. Qualitative analysis of three randomized controlled trials in peripheral nerve repair

3.3.1. Significance of age

No significant difference in age were observed between the test and control groups ($P = .98$; Fig. 2).

3.3.2. Significance of type of injury

Type of injury is a major factor which influences the outcome of the sensory recovery. Therefore, type of injury was studied for the qualitative analysis and the results follow (Fig. 3). Between the two types of nerve injury, cut and other types, a qualitative analysis was performed using Rev. Man 5.1 software. Most of the patients were injured due to the deep cut injuries. But overall difference was limited.

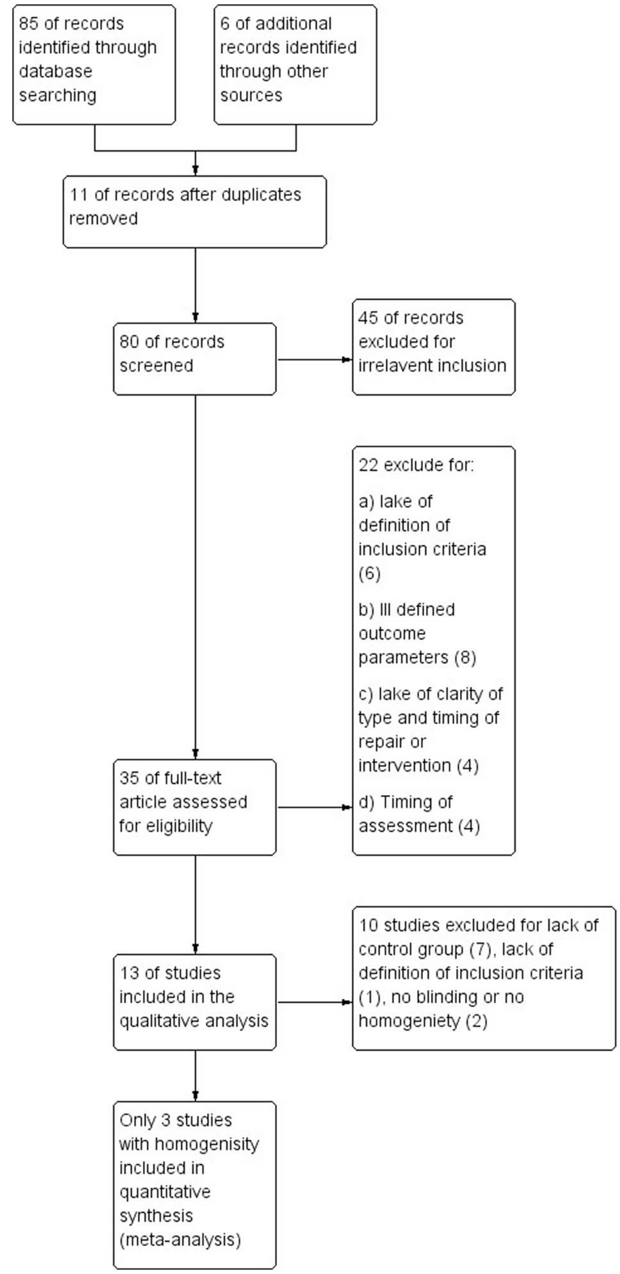

Fig. 1. PRISMA flow diagram of the included studies.

3.3.3. Qualitative analysis of the efficacy of conduits vs. conventional sutures for sensory outcome

Total 300 patients data have been analysed for the qualitative effect of the sensory recovery of the patients after nerve injury and the results are as follows (Fig. 4). Significant improvement in sensory recovery was observed in the conduits treated group compared to the conventional sutures treatment. Odds ratio significantly favor the conduits group (3.78; $P < .00001$) Test results for overall effect was found to Z = 5.64 (Fig. 4).

Table 1
Comparison of three randomized control trials in peripheral nerve repair.

S. No	Study characteristics	Aberg2009		He2013		Weber2000	
		Test	Control	Test	Control	Test	Control
1	# Age group (Years, Mean ± SD) Range	36 ± 17 15–58	26 ± 10 15–41	33 ± 11 18–61	37 ± 14 15–77	36 ± 14 17–65	34 ± 14 17–65
2	Sample size	$n = 5$	$n = 6$	$n = 72$	$n = 81$	n = 81	n = 81
3	Follow-up length	18 months for primary outcome; 2 weeks, 3, 6, 9, 12 months for secondary outcomes		1, 3 and 6 months		3, 6, 9 and 12 months	
4	# Nerves injured and location and type of injury	Median and/or ulnar nerves; Complete; at the wrist/forearm level		Digital sensory nerves at thumb, index, ring, little fingers, radial and ulnar nerves		Median and ulnar Digital sensory nerves supplying palmar aspect; Complete; Sharp cut, knife and crush injuries at the level of palm	
5	Inclusion criteria	Complete Nerve injury at the wrist/forearm level; Operated within 1 week after injury; No significant past medical and/or surgical history		Complete Digital nerve injury; Age group: 14–80 years; a nerve defect that was 1-5 cm in length; Operation in < 6 months; Exclusion criteria: acute infection, severe wound contamination, unstable vital signs, and inability to conduct a functional assessment of nerve repair due to damage to the skin; neurological and other diseases such as diabetes that could potentially affect the nervous system; chronic diseases causative of neuropathy; inability to comply with treatment, postoperative rehabilitation and follow-up; and a defect > 5 cm; neurological or autoimmune disease during the trial		Complete division of sensory nerves distal to the distal wrist crease with gap of < 3 cm; not nerves supplying dorsal aspect; 17–75 years; Excluded diabetic, alcoholic, gout or collagen vascular disease, and those receiving treatment with immunosuppressive drugs.	
6	Intervention	Resorbable poly[(*R*)-3-hydroxybutyrate]	Conventional direct Suture	Digital nerve repair with hANG	Conventional direct tension-free suture	Polyglycolic acid conduit	Standard repair, either end-to-end or with a nerve graft,
7	Statistical method	Groups compared using the change in percentage of function in affected hand compared to normal hand function with Wilcoxon rank- sum test; Fisher's exact test for comparison hand function with dichotomisation of outcome results based on Mackinnon-Dellon scale for stratification of 2PD results		Non-inferiority study comparing Test group minus control group satisfaction rate and 95% CI for S-2PD at nerve and patient levels; Groups also compared using the adjusted centre effect, the Cochran- Mantel-Haenszel chi-square test, the 95% CI		Percentages of nerves with excellent results in both groups were compared using the chi-square test or Fisher's exa*ct*-test as appropriate for the sample sizes. The OR on odds of an excellent result for those in the conduit group with those in the control group. Multiple logistic regression to adjust the odds ratio for other factors; The mean moving two-point discrimination was compared using the two-sample t-test	
8	# Primary outcome measures	static 2-point discrimination test (s2PD)[a] at 18 months		static 2-point discrimination (s2PD)[a] and Semmes-Weinstein (SW) monofilament examination by Touch-Test at 6 months		Static and moving 2-pointt discrimination (s/m2PD) methods at 12 months	
9	Secondary outcome measures	Motor: British Medical Research Council score, manual muscle test, grip and pinch strength, motor ENG and needle EMG parameters Sensory: Sensory ENG, thermal thresholds Social: four-question form, the sensorimotor test and the Sollerman hand-function test		Mean time from injury to repair;		Sensory: Graded sensory return Complications: Pain and return to work; s/m2PD) methods at 12 months	
10	Results	No significant differences between the treatment groups		hANG is a safe and more effective for the repair of nerve defects of 1–5 cm in size		There was no significant difference in outcome between the two groups as a whole. The percentage of nerve repairs with excellent outcome was 43.5% (20 of 46) of the conduit repairs and 42.8% (24 of 56) of the standard repairs (p = .46). Polyglycolic acid conduit offers more improved sensation, compared with current end-to-end repair techniques.	

[a] Measured by a touch-test of two point discrimination and Semmes-Weinstein (SW) monofilament examination by touch-test sensory evaluators. # Parameters included for the meta-analysis, since other parameters did not pass the homogeneity test ($P < .05$).

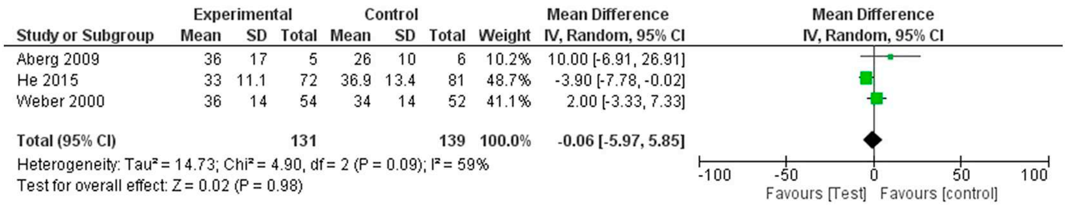

Fig. 2. Qualitative analysis of the distribution of age of patients between test and control group using Rev. Man 5.1 software.

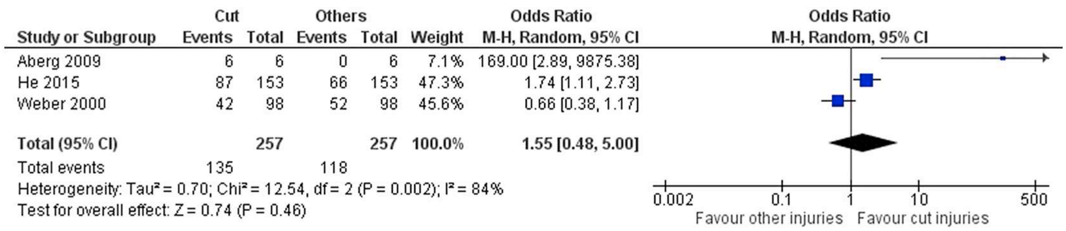

Fig. 3. Qualitative analysis of the type of injury among the patients between test and control group using Rev. Man 5.1 software.

4. Discussion

Starting with the initial screening on 91 reports, only 3 reports Berg2009, He2013 and Weber2000 could be selected for the qualitative analysis. Many published works did not explain properly about the outcome and follow-up period after surgery, therefore three series with the defined outcome only selected for the analysis. Randomized trials with clear definition of outcome and minimum 6 months follow-up period only were selected for the final analysis. Three randomized trials included 263 patients who were qualitatively analysed for the efficacy of conduits in peripheral nerve repair using sensory recovery as the common outcome parameter.

In these selected three series (Aberg2009, He2013 and Weber2000) [20,34,35], patients were recruited within the age group of 14–38 years and the difference of age group between the cases and control was almost similar (Table 1; Fig. 2). The weighted odd's ratio for male gender between the conduits and sutures groups was 1.63, with wide confidence intervals of 0.74 and 3.58 ($P = .22$), with homogenous distribution between the three study groups. ($P = .35$). An earlier study reported that it was the female patients who had better recovery after the repair of pure sensory nerve injuries compared to male patients [35].

All three series used sensory discrimination as primary outcome measure, s2PD, measured by a two point discrimination touch-test along with/without SW monofilament touch-test for the assessment of sensory recovery. The s2PD and SW are the gold standard neurosensory tests being practiced in nerve injury clinics [36–38] for the assessment of sensory recovery in patients and which is another important reason to select these three series for the final qualitative analysis. At the s2PD method, patients will be discriminated based on the recovery of sensitivity and scored as S0 (no recovery of sensibility in the autonomous zone of the nerve), S1 (recovery of deep cutaneous pain sensibility), S2 (recovery of superficial pain and some sensibility), S3 (recovery of pain and touch sensibility with disappearance of over-response) and S4 (complete recovery). In the current study of meta-analysis of sensory recovery from peripheral injuries, only S3 and S4 grade patients were considered for the final analysis since all three studies recruited these groups. Though, S2 grade of sensory recovery showed sensitivity recovery from the peripheral injury, it does not included in the final analysis because of the pain and discomfort. Berg2009 series did not found any significant different between test and control, a series which had only limited number of participants.

Two different type of conduits were used in the selected 3 studies. Aberg2009 and Weber2000 used biodegradable polymers such as poly [(*R*)-3-hydroxybutyrate] (PHB) conduits in a tube-like structure and sealed with fibrin glue, whereas, He2013 used human acellular nerve graft (hANG) and compared it with the effect of direct tension free sutures. In all three studies, effect of conduits were compared with the effect of epineural end-to-end suturing or tension free suturing method. All three studies showed similar effect on the efficacy of the conduits compared to conventional sutures. However, it requires additional studies to identify the best types of effective conduits in peripheral nerve regeneration. The quantitative analysis of the Berg2009, He2013 and Weber2000 shows significantly higher improvement in sensitivity recovery after conduits treatment compared to the conventional sutures. Overall, test results show Z = 5.64 ($P < .00001$), which is significant.

Only two of our selected three studies addressed the issue of nerve gaps as a consideration. The study by Aberg et al… did not mention about the nerve gap element in their study patients and control. In the paper by He et al, the mean length of the never grafts was 1.8 ± 0.82 cm with a range of 1–5 cm but there was no clear information on whether this applies to whole group or to the test or the control group. Further, it was mentioned that the length of the conduits were of 3 sizes 0.20 ± 1, 40 ± 1 and 60 ± 1 mm in length. The number of cases on which they were used or their differential association with the outcome had not been mentioned. In the study by Weber et al., patients with < 3 cm nerve gaps only were recruited into

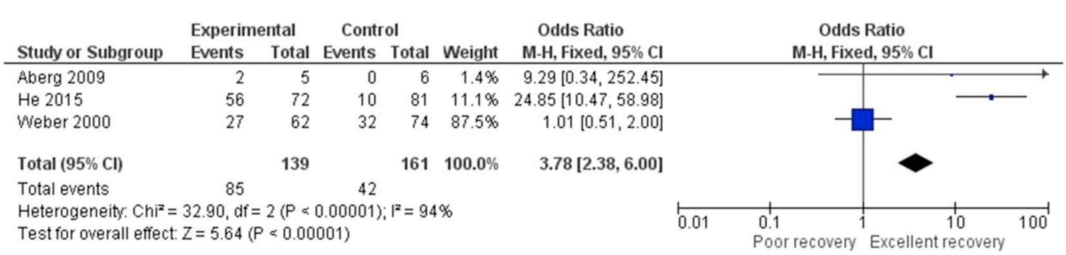

Fig. 4. Qualitative analysis of the sensory recovery after nerve injury among the patients between test and control group using Rev. Man 5.1 software.

study. Even for subjects with nerve gap 5–7 mm, end-to-end suturing was done without grafts. When gap was above 7 mm, nerve graft was done for the suture group. The nerve conduits repair gave better results than standard end to end repair when the nerve gap is 4 mm or less. In this 5–7 mm gap group, there was no significant difference between suture and conduit groups. Above 12 mm, the suture group, appeared to fare better than the conduit group. However, when the two groups were analysed as whole was analysed with respect to the nerve gap there was no significant difference between them. Due to lack of homogeneity in the available data between these three studies, no meta-analysis could be performed with respect to the influence of nerve gap on the outcome between suturing vs conduits".

A limitation of the study is, the final meta-analysis were carried out for only with 3 series. However reaming 88 records from the total 91 were rejected because of stringent inclusion and exclusion criteria of this study especially robustness of study such as RCT, minimum follow-up period etc. The study results did not give evidence for superiority of conduits over end-to-end sutures and indicated the need conduct more clinical trials on the effect of conduits on peripheral nerve recovery, perhaps with superiority models. Further, RCT data on nerve injury repair other than that of hands are limited. But it is presumable that lower limb sensory nerve (Sural/saphenous) repair outcome could be similar. However, the outcome analysis is readily discernible only for sensory nerves. All three RCTs analysed have tested only digital sensory nerves, and it is also well-known that the biological properties of motor nerve fibres differ from sensory fibres. Therefore one must exercise caution in extrapolation of the findings of this meta-analysis onto mixed or pure motor peripheral nerve injuries. Further studies are needed to determine the outcome of various types of nerve repair techniques on motor or mixed nerve injuries. Further, this metaanalysis also do not provide adequate data on innervation density, adverse effects like neuromas, hyperesthesia, cold intolerance and pain.

Several neurotropic factors known as nerve growth factors had shown synergistic effect on the enhancement of survival, differentiation and growth of the neurons during regeneration of injured nerve and thus enhance the repair process of nerves [39]. Specific growth factors have been delivered often using implantable osmotic pumps or instilled into the site of nerve injury using a variety of carriers including gel foam [8], fibrin glue [40], and genetically engineered cells such as Schwann cells [41] and fibroblasts. Growth factors can also be incorporated into the matrix substance within the guidance conduit [41]. With these further exciting prospects, the repair of nerve injuries is entering new frontiers in research which may eventually give insights into management of CNS injuries as well.

5. Conclusion

A meta-analysis of three quality randomized clinical trials designed to compare the effect of conduits with conventional sutures, showed that conduits were safe and significantly more effective when compared to conventional sutures in effecting repair of sensory nerve injuries. More studies are needed to verify whether this better efficacy is applicable to motor and mixed nerves as well as to deeper peripheral nerves or cranial nerves and more complex components of nerve plexuses. It is presumable that well-designed animal trial experiments followed by human clinical trials, with leads from the best evidences from basic sciences will help establish better techniques in future, making human nerve repairs more efficient and effective, and thereby lowering disabilities.

Conflict of interest

The Authors have no conflict of interest

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