SCIENTIFIC ARTICLE

Autologous Fibrin Glue Versus Microsuture in the Surgical Reconstruction of Peripheral Nerves: A Randomized Clinical Trial

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Purpose This study compared the motor and sensory recovery and the operative time of autologous fibrin glue application with conventional microsuturing technique in repairing peripheral nerves at the forearm and wrist levels

Methods Eighty-five patients with injuries of the median, ulnar, or both nerves at the wrist and forearm levels underwent nerve repair between September 2014 and June 2018. Patients were randomly assigned at the time of diagnosis to a microsuture group (42 patients), in which standard epineurial microsurgical suturing was performed, or a fibrin glue group (43 patients), in which nerve repair was performed using autologous fibrin glue. The primary outcome measure was motor and sensory recovery. Operative time was the secondary outcome measure. Other outcome measures that were added *post hoc*, after trial initiation, included time to motor and sensory recovery; grip strength; pinch strength; Michigan hand outcome score; amplitude, latency, and duration of the compound motor unit action potential; and complications. All patients were followed up a minimum of 1 year.

Results At the final follow-up, both groups had regained similar motor and sensory function. The mean operative time was shorter in the fibrin glue group. Both groups had similar amplitude, latency, and duration of the compound motor unit action potential. Michigan Hand Outcome scores and mean percent recovery of grip strength and pinch strength were also similar. Six of 43 patients in the fibrin glue group compared with 8 of 42 patients in the microsuture group developed postoperative complications.

Conclusions The use of fibrin glue to repair peripheral nerves is as effective as microsuturing in regaining motor and sensory functions and is associated with shorter operative time. *(J Hand Surg Am. 2022;47(1):89.e1-e11. Copyright © 2022 by the American Society for Surgery of the Hand. All rights reserved.)*

Type of study/level of evidence Therapeutic II.

Key words Autologous donation, fibrin glue, microsuture, peripheral nerve.

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Nonabsorbable microsuturing is traditionally used for accurate approximation of nerve ends in peripheral nerve repairs because it offers precise coaptation of nerve ends, maintenance of the tensile strength of the repair, and a low risk of gap formation or repair rupture.[1] However, drawbacks include foreign body reaction and impairment of intraneural microvascularization as a result of suture tension from knot tying, which, in turn, might interfere with the quality of the axonal regeneration.[2] Therefore, outcomes are often disappointing.[3] Microsurgical repair is also time consuming and requires appropriate surgical skills.[4,5] Consequently, some studies have suggested the use of sutureless methods such as fibrin glue because they may also increase the number of Schwann cells at the repair site during the 3-month postoperative interval, an essential step in nerve regeneration[5] and functional recovery.[6,7]

Fibrin glue is a 2-component sealant (concentrated fibrinogen obtained by cryoprecipitation and thrombin) derived from whole blood, which, when mixed, reproduces the final pathway of blood coagulation to form a viscous adhesive that maintains tissue approximation.[8,9] Fibrin glue results in reduced local inflammation and scar tissue formation at the repair site and a faster regeneration time.[4,5,10] Additionally, autologous fibrin glue contains large amounts of various platelet-derived growth factors, which are associated with an increased number and diameter of regenerated nerve fibers compared with those associated with bovine commercial fibrin glue.[11] Fibrin glue can also decrease operative time and help maintain proper nerve orientation, potentially improving recovery.[12,13]

Although fibrin glue has been in clinical use for many years, there is a lack of literature reporting well-controlled clinical trials regarding its use in humans for peripheral nerve surgery, despite the predominance of experimental studies evaluating its role in animal models. The purpose of this study was to compare functional outcomes and the operative time of autologous fibrin glue application and conventional microsuturing in the repair of injured peripheral nerves at the forearm and wrist levels.

MATERIALS AND METHODS

Study design

The study was prospectively conducted between September 2014 and June 2018 as a randomized clinical trial (Pan African Clinical Trial Registry ID: PACTR201409000879274) after being approved by our institutional research board.

Participants

Eighty-five patients were enrolled in the study (Fig. 1). Patients enrolled in the study were older than 18 years; with complete division of the ulnar, median, or both nerves at the forearm or wrist level; treated within 3 months after injury; and required either direct repair or nerve graft. Exclusion criteria were partial injuries; brachial plexus palsies; injuries expected to recover spontaneously (neuropraxia and axonotmesis); injuries with nerve gaps longer than 5 cm; entrapment syndromes; and established chronic illnesses that could affect joint motion, nerve healing, or patient compliance. Patients with previous surgery in the hand or medical contraindications to surgery were also excluded.

Our patients (mean age 36.2 [20−58] years) were eligible for autologous blood donation according to the European guidelines for autologous transfusion.[14] These guidelines defined age limits for donation as a minimum of 18 years and maximum of 65 years. An autologous donation was not collected from persons weighing less than 50 kg or having blood hemoglobin levels below 11 g/dL. Any patient with unstable cardiac or infectious diseases or alcohol/drug intoxication was deferred from donation and was not included in the study. The autologous blood was the source of fibrin glue for our patients. An amount not exceeding 500 mL was collected for its preparation.

Patients were randomly assigned to 1 of 2 groups using sealed white envelopes containing the group allocation for each case, produced by an independent epidemiologist not directly involved in the study. The surgeon opened the envelope on the day of admission. Participants were enrolled and randomized at the time of diagnosis, prior to surgery, and no participant was recruited after surgery. In the microsuture group (42 patients), a standard epineurial microsurgical repair was performed. In the fibrin glue group (43 patients), patients underwent a nerve repair using autologous fibrin glue. All patients completed a minimum of a 12-month follow-up period.

Description of treatment

Surgical technique: In a supine position with the hand and forearm on a hand table and a pneumatic tourniquet on the affected extremity, both ends of the injured nerve were exposed and gently mobilized. They were trimmed until a normal fascicular pattern was observed. The epineurium was identified circumferentially. Proper orientation of both ends relied on identifying the topography of both sides and the

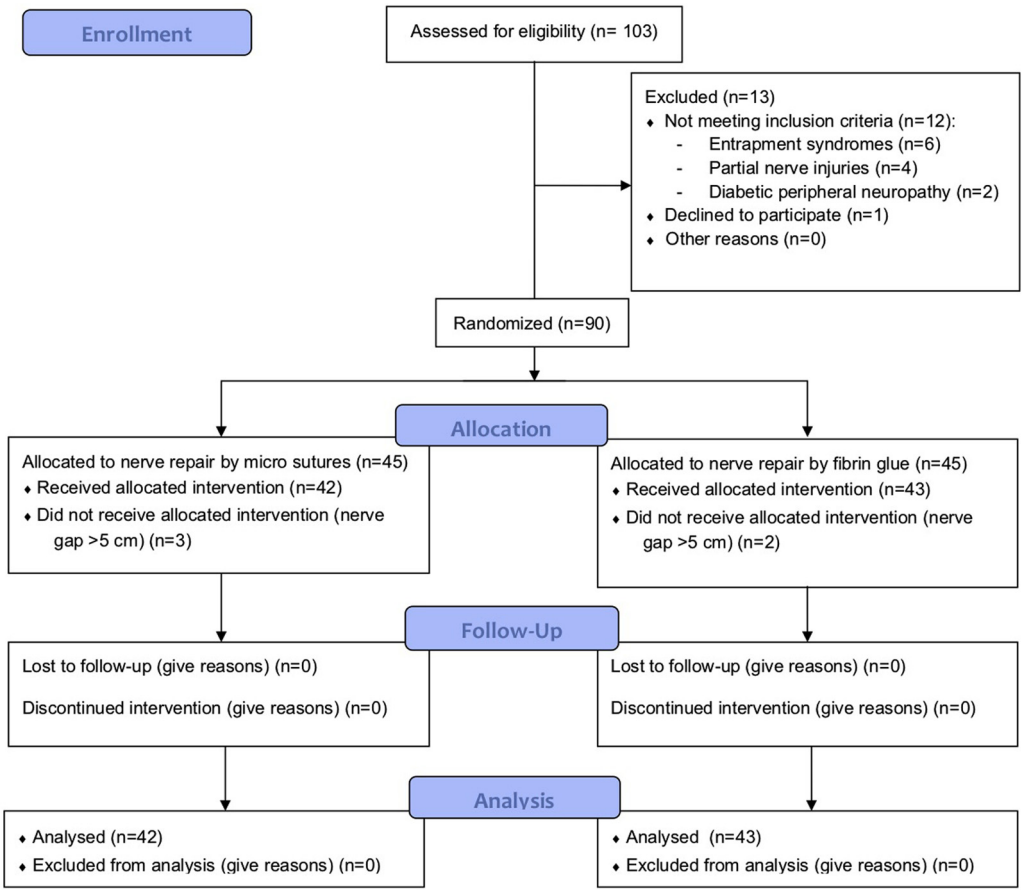

FIGURE 1: The CONSORT flow diagram shows the progress of subjects at each stage of the clinical trial. CONSORT, Consolidated Standards of Reporting Trials.

longitudinal blood vessels on the surface of the nerve. Both ends were approximated using jeweler's forceps to ensure a tension-free repair. In the microsuture group, the repair was performed by a standard epineurial microsurgical technique using 8/0 and 9/0 nylon sutures. In the fibrin glue group, autologous fibrin glue was used. In patients with extensive scarring or a painful neuroma (Fig. 2A, B), external neurolysis was performed, and the neuroma and fibrous tissue were excised until healthy fascicles were clearly seen under magnification occupying the whole surface of both nerve ends. The resulting gap was covered by a 6-cabled graft for the median nerve and 4-cabled graft for the ulnar nerve, using the sural nerve as a donor. In the microsuture group, the graft and both ends of the nerve were coapted with microsutures. In the fibrin glue group, the cables were glued together with a few drops of fibrin glue, which was applied to coapt the graft to both proximal and distal ends of the injured nerve (Fig. 2C, D). The glued repair sites were wrapped by a layer of oxidized regenerated cellulose knit.

Autologous fibrin glue preparation: One unit of blood was collected from patients 3 days prior to surgery for patients assigned to the fibrin glue group. Approximately 450 mL was collected in triple blood bags containing 63 mL CPDA-1 (2.0 g dextrose, 206 mg citric acid, 140 mg monobasic sodium phosphate, and 17.3 mg adenine) (JMS). The plasma was separated from the red blood cells within 2 hours by centrifugation (Thermo Sorvall RC 12BP, Thermo Fisher Scientific) at 4,000 rpm for 10 minutes. The plasma was frozen and stored for 48 hours at −40 °C. Then, fresh frozen plasma was thawed at 4 °C for 8 hours before centrifugation at 4,000 rpm for 10 minutes, and the supernatant plasma was transported to the other satellite bag. The cryoprecipitate was suspended in 15 mL of plasma. Five milliliters of fibrinogen and factor XIII containing precipitate was drawn into a syringe. This composed Component 1. One hour before the operation, 10 mL of blood was collected from the patient in plain tubes, set aside at room temperature until clotting, then centrifuged at 3,000 rpm for 10 minutes. The supernatant (thrombin) was collected,

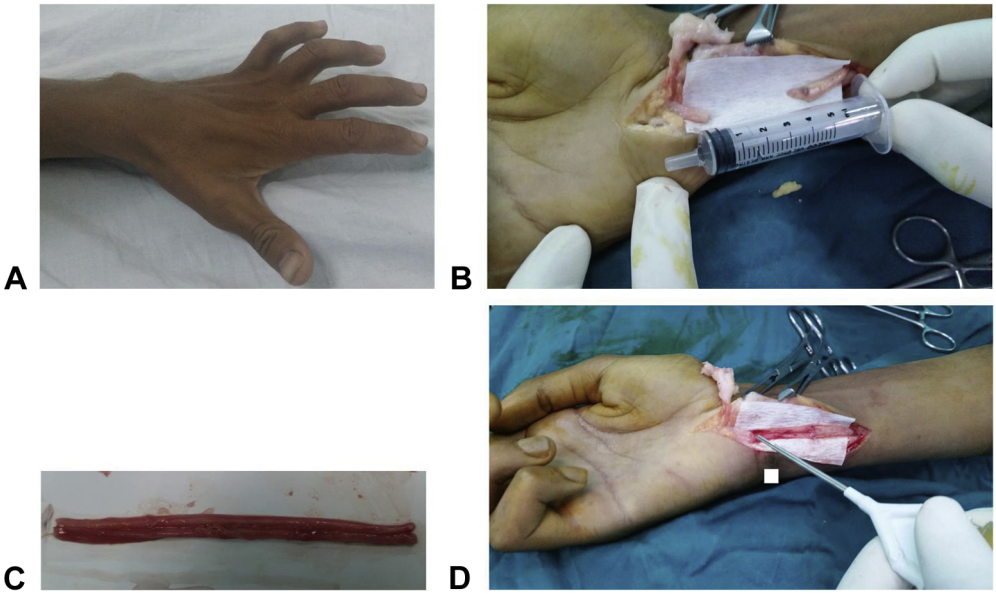

FIGURE 2: The graphs show the autologous fibrin glue application. **A** A 39-year-old teacher presented with a 2-month ulnar nerve injury at the wrist level. **B** A 3-cm nerve gap was produced after excision of a painful neuroma. The graph shows the 2 components of the fibrin glue (cryoprecipitate and thrombin). **C** The graft cables were held together by fibrin glue. **D** The graft was repaired to the proximal and distal nerve stumps by the use of fibrin glue.

which comprised Component 2.[15,16] A second syringe (Component 2) contained 5 mL of autologous thrombin and 1.5 mL of calcium gluconate solution (50 mg/mL calcium gluconate monohydrate). Both components were warmed for 10 minutes at 37 °C. The syringes were placed into a double-chambered applicator. The components were slowly combined and simultaneously dripped onto, and around, the repaired nerve until the repair site was adequately sheathed. After 5 minutes, the coagulum became firm enough to start wound closure. Fibrin glue preparation was performed by the third author (a consultant clinical pathologist) in our hospital blood bank.

Aftercare

The same postoperative protocol was applied to all patients. On the third postoperative day, dressings were removed. The repair sites were protected using splints for 3 weeks after surgery, then passive stretching exercises were started. Electrical stimulation was initiated for both groups after 6 weeks. Thirty to 60 pulses per second in a surge mode were applied. The on time was 10 seconds,[17] and the off time was 30 seconds.[18] To strengthen the muscle power, it was given progressively increasing resistance, ie, gravitational or manual. Treatment time lasted 15 to 20 minutes daily, utilizing a high frequency (30 Hz) alternating current, until voluntary muscle contraction was visible. This protocol was performed by 2 senior hand therapists 5 days/week over 6 weeks.[17–20] Following reinnervation, movement and strengthening exercises were added. Patients were also provided instructions for self-directed home exercises.

Outcome measures

Our primary outcome measure was motor and sensory recovery. Operative time was the secondary outcome measure.

Clinical evaluation: Muscle power and sensory recovery were assessed using the modified British Medical Research Council (MRC) scale.[21,22] Functional motor recovery was considered useful when a grade of M3 or more was achieved, and functional sensory recovery was considered useful when a grade of S3 or more was regained.[23,24] The Tinel sign and 2-point discrimination were used to evaluate the progress of nerve regeneration at 6 and 12 weeks after surgery and at 3-month intervals thereafter. Operative time for the microsuture group was the time required for the placement of 6 epineurial sutures; while for the fibrin glue group, it was the time necessary for sealant application, plus a standard setting time of 5 minutes.

Electrophysiologic evaluation: Nerve conduction studies were performed to document nerve injuries prior to surgery and to detect signs of regeneration at 6 weeks, 3 months, and 1 year after surgery. Reinnervation was assessed by the amplitude, latency, and duration of the compound motor unit action potential (cMUAP).[25]

TABLE 1. Patients' Demographic and Clinical Data

Demographic and Clinical Data	Microsuture Group	Fibrin Glue Group
Number of patients	42	43
Mean age, y	35.9 (21–58)	36.5 (20–58)
Male/female	27/15	29/14
Operated right/left hand	36/6	36/7
Affected dominant/nondominant hand	37/5	36/7
Affected nerve		
Ulnar	18 (42.9%)	19 (44.2%)
Median	14 (33.3%)	13 (30.2%)
Combined median and ulnar	10 (23.8%)	11 (25.6%)
Associated injuries		
Ulnar artery	13 (31%)	14 (32.6%)
Flexor carpi ulnaris	15 (35.7%)	16 (37.2%)
Flexor digitorum superficialis	12 (28.6%)	11 (25.6%)
Flexor digitorum profundus	8 (19%)	9 (20.9%)
Palmaris longus	9 (21.4%)	8 (18.6%)
Radial artery	2 (4.8%)	2 (4.6%)
Type of surgery		
Direct primary nerve repair	25 (59.5%)	27 (62.8%)
Nerve grafting/secondary repair	17 (40.5%)	16 (37.2%)
Mean time from injury to surgery, d		
Direct primary nerve repair	4.5 (3–7)	5 (3–7)
Nerve grafting/secondary repair	37 (20–75)	39 (20–80)
Mean follow-up period, mo	14.5 (12–18)	15.2 (12–18)

Electromyography and the MRC scale were used to evaluate the recovery of abductor pollicis brevis and flexor pollicis longus for the median nerve, and abductor digiti minimi for the ulnar nerve.

Functional evaluation: Grip and pinch strengths (in Kg) were measured by a Jamar hydraulic hand dynamometer and pinch gauge (Saehan Corporation). Recovery of these parameters was calculated by dividing the postoperative grip and pinch strengths of the affected hand to those of the contralateral healthy hand, then multiplying by 100. For right-handed individuals, it was assumed that the dominant hand would normally be 10% stronger than the nondominant hand. No correction was made for left-handed individuals.[26] All patients completed the Michigan Hand Outcome questionnaire at 1 year postoperatively.[27]

Statistical analysis

A sample size of 42 patients in each group allowed the demonstration of a 24% difference in the percentage of patients achieving grade M3 or more at an alpha level of 0.05 and power of 80%.[28] Statistical analyses were conducted according to the intention-to-treat principle. Data were initially assessed for normality by the Shapiro-Wilk test, and variances were shown to be equal by Levene's test. The chi-square (χ^2) test was used to compare proportions. The Fischer-Exact test was used instead of the χ^2 test when any variable value was less than 5. A P value of less than .05 was considered statistically significant.

RESULTS

Initially, 103 patients presented with median, ulnar, or both nerves injured at the wrist and forearm levels. Twelve patients were excluded from the study because of entrapment syndromes (n = 6), partial nerve injuries (n = 4), and diabetic peripheral neuropathy (n = 2). One patient declined to participate. Another 5 patients who were initially enrolled were excluded because they were found to have a long nerve gap intraoperatively (6–10 cm). A total of 85 patients remained (42 in the microsuture group and 43 in the fibrin glue group) available for analysis (Fig. 1).

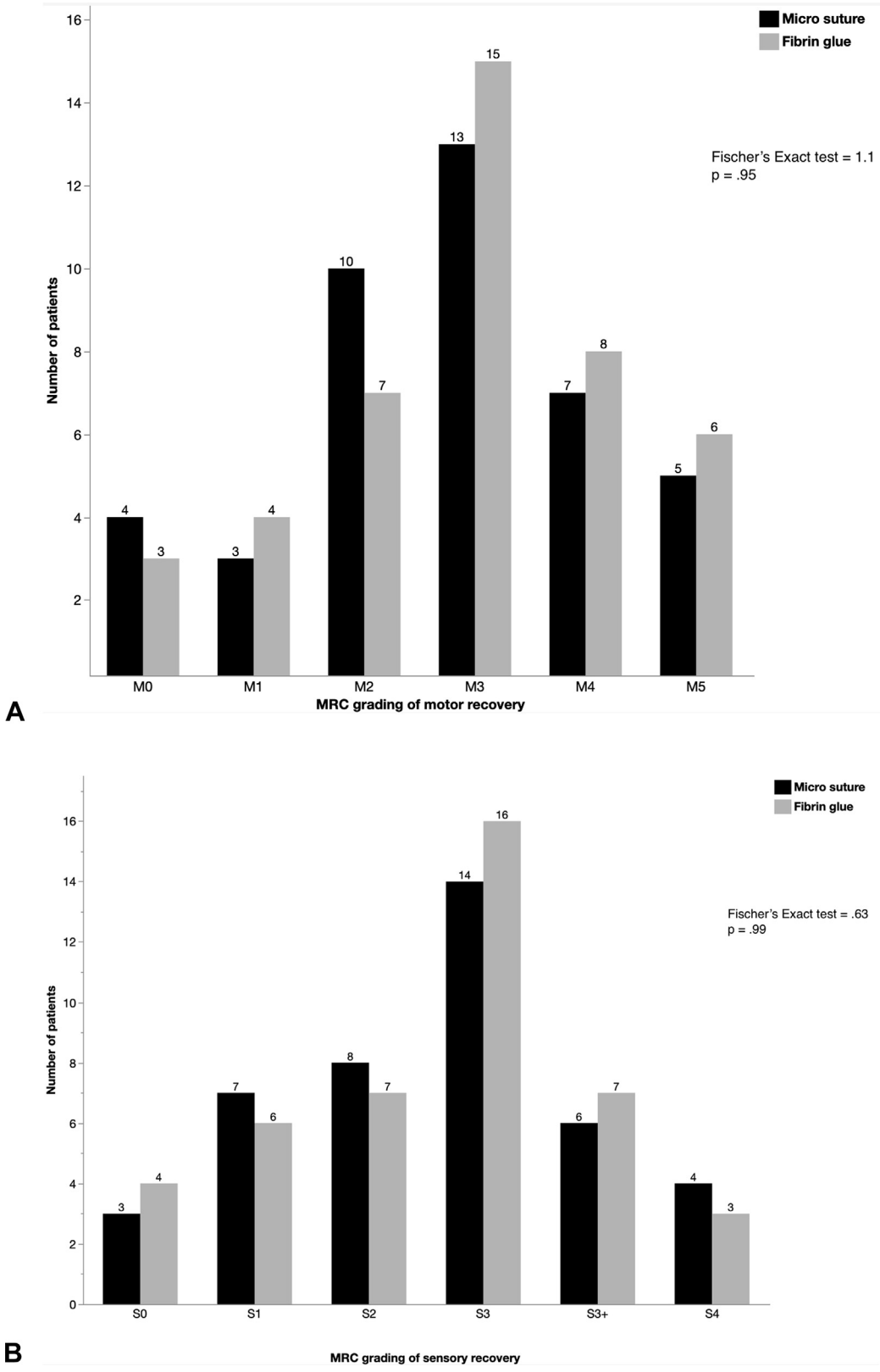

FIGURE 3: A Motor recovery of both groups at final follow-up. **B** Sensory recovery of both groups at final follow-up.

Both groups had similar demographic and clinical characteristics (Table 1). The mean follow-up duration was 14.9 (12−18) months. The mean time from injury to surgery was 4 (3−7) days for patients who underwent direct primary nerve repair and 38 (20−80) days for

TABLE 2. Comparison of the Useful Motor and Functional Recovery According to the Injured Nerve Between Both Groups, No. (%)

No., %	Microsuture Group				Fibrin Glue Group			
	Median nerve (n = 14)	Ulnar nerve (n = 18)	Combined (n = 10)	Total*	Median nerve (n = 13)	Ulnar nerve (n = 19)	Combined (n = 11)	Total*
Motor recovery								
Useful†	9 (64.3)	12 (66.7)	4 (40)	25 (59.5)	12 (92.3)	13 (68.4)	4 (36.4)	29 (67.4)
Not useful	5 (35.7)	6 (33.3)	6 (60)	17 (40.5)	1 (7.7)	6 (31.6)	7 (63.6)	14 (32.6)
Sensory recovery								
Useful‡	9 (64.3)	11 (61.1)	4 (40)	24 (57.1)	11 (84.6)	11 (57.9)	4 (36.4)	26 (60.5)
Not useful	5 (35.7)	7 (38.9)	6 (60)	18 (42.9)	2 (15.4)	8 (42.1)	7 (63.6)	17 (39.5)

*Chi-square test was performed for the total values of motor ($\chi^2 = 0.57$, $P = .45$) and sensory recovery ($\chi^2 = 0.09$, $P = .76$) in both groups.
†Useful motor recovery is defined as grade M3 or more.
‡Useful sensory recovery is defined as grade S3 or more.

those who underwent nerve grafting or secondary repair (Table 1).

At the final follow-up, both groups regained similar motor and sensory functions ($P = .95$ and $P = .99$, respectively) (Fig. 3). Useful motor recovery (ie, grade M3 or greater) was achieved in 25 of 42 patients in the microsuture group compared with 29 of 43 patients in the fibrin glue group ($P = .45$). Similarly, useful sensory recovery was achieved in 24 of 42 patients in the microsuture group compared with 26 of 43 patients in the fibrin glue group ($P = .76$) (Table 2). Four patients in the microsuture group and 3 patients in the fibrin glue group failed to regain any motor power improvement at the final follow-up (Fig. 3A). Three patients in the microsuture group and 4 patients in the fibrin glue group failed to regain any sensory recovery at the final follow-up (Fig. 3B). Regarding the type of surgery, whether primary repair or nerve graft/secondary repair, both groups had similar motor and sensory recovery (Table 3).

Mean operative time of repair was shorter in the fibrin glue group (6.8 [6−8] minutes) than in the microsuture group (22 [20−26] minutes).

Additionally, the 2 groups were similar in terms of mean percent recovery of grip and pinch strengths and Michigan Hand Outcome scores (Table 4).

The median amplitude, latency, and duration of the cMUAP of the median and ulnar nerves were similar for both groups (Table 5).

In the fibrin glue group, 2 patients developed superficial wound infection, and 4 patients experienced fixed deformities of the fingers due to soft tissue contracture. In the microsuture group, 2 patients had superficial wound infection, and 6 patients experienced fixed deformities.

DISCUSSION

Although we achieved similar motor and sensory recovery, grip and pinch strengths, and Michigan Hand Outcome scores in both groups at the final follow-up, the patients treated with fibrin glue had shorter operative times. No major complications occurred in either group.

Our findings matched several experimental and human studies. In a rat sciatic nerve model, Menovsky and Beek noted no difference in the recovery of motor functions among the suture, fibrin glue, or laser repair groups.[29] Similarly, Moy et al[30] reported similar gait patterns or flexor muscle tone reduction between the fibrin seal and suture groups for repairing the tibial nerve in their rabbit model. In their human study, Egloff and Narakas[31] reported favorable results of

TABLE 3. Comparison of the Useful Motor and Functional Recovery According to the Type of Surgery Between Both Groups, No. (%)

No., %	Microsuture Group		Fibrin Glue Group		*P* Value*
	Primary repair (n = 25)	Nerve graft/secondary repair (n = 17)	Primary repair (n = 27)	Nerve graft/secondary repair (n = 16)	
Motor recovery					
Useful†	20 (80)	5 (20)	21 (72.4)	8 (27.6)	.52
Not useful	5 (29.4)	12 (70.6)	6 (42.9)	8 (57.1)	.44
Sensory recovery					
Useful‡	19 (79.2)	5 (20.8)	17 (65.4)	9 (34.6)	.28
Not useful	6 (33.3)	12 (66.7)	10 (58.8)	7 (41.2)	.79

*Chi-square test was performed.
†Useful motor recovery is defined as grade M3 or more.
‡Useful sensory recovery is defined as grade S3 or more.

TABLE 4. Postoperative Functional Outcomes in Both Groups, Mean (Range)

Outcome	Microsuture Group (n = 42)	Fibrin Glue Group (n = 43)
Mean percent of grip strength recovery		
Postoperative grip strength (kg)	73.2 (52–80)	72.4 (50–84)
Postoperative tip pinch strength (kg)	80 (57–92)	79.1 (57–90)
Postoperative side pinch strength (kg)	69.6 (43–86)	70 (43–88)
Postoperative palmar pinch strength (kg)	71.9 (43–97)	72.8 (43–98)
MHO scores		
Hand function	64.1 (50–70)	64.6 (55–72)
Activities of daily living	70.2 (60–75)	70.3 (60–74)
Work	69.2 (55–80)	70.4 (50–78)
Pain	49.3 (40–58)	50.6 (45–55)
Aesthetic appearance	66.4 (55–70)	65.9 (55–75)
Satisfaction	70.3 (60–75)	70.8 (62–76)
Total MHO score	63.5 (60–67)	64.6 (61–68)

MHO, Michigan Hand Outcome.

peripheral nerve reconstructions using fibrin glue in 56 patients who underwent free functional muscle transfer, brachial plexus reconstruction, major peripheral nerve reconstruction, and digital nerve reconstruction. However, the heterogeneity of their clinical circumstances made it difficult to compare their results with the described results of microsuturing.[31] Another 2 human studies compared the use of fibrin glue with conventional microsuturing while treating patients with upper extremity peripheral nerve injuries by either direct neurorrhaphy or nerve grafting. These studies reported similar outcomes in both groups regarding the motor and sensory recovery, but, as in our study, with a significantly shorter operative time using fibrin glue.[28,32]

Cruz et al[1] reported that both fibrin and suture groups in all histological sections had an inflammatory reaction and scar tissue formation. However, this inflammatory response in the nerve tissue was associated with glue of a bovine source. Therefore, in our study, we used fibrin glue that was prepared from the patient's own blood. Additionally, we ensured meticulous hemostasis before applying the glue to allow for optimal adherence, and we left the glue components undisturbed for 5 minutes in situ to allow for adequate coagulum sealing.

Some studies claimed that the main drawback of the use of fibrin glue was the low tensile strength of repair that could lead to gapping and repair failure.[1,33,34] However, 2 biomechanical studies

TABLE 5. Comparison of the Amplitude, Latency, and Duration of the Compound Motor Unit Action Potential of the Median and Ulnar Nerves Between Both Groups, Median (Range)

	Microsuture Group		Fibrin Glue Group	
cMUAP	Median nerve (n = 24)	Ulnar nerve (n = 28)	Median nerve (n = 24)	Ulnar nerve (n = 30)
Amplitude, mV	4 (3−6)	3.75 (3−5)	4 (3−5)	4 (3−5)
Latency, mS	4.5 (4−7)	5 (4−7)	5 (4−6)	5 (4−7)
Duration, mS	9 (8−12)	9 (8−12)	8 (8−12)	9 (8−12)

confirmed that the low tensile strength of fibrin glue repair was present only during the early postoperative period; 2 weeks and later after surgery, repair with fibrin glue and microsuturing had equivalent resistance to gapping, with no differences in peak load.[10,35] Also, there was no risk of gapping when using fibrin glue in tension-free repairs.[36]

Being prepared autologously, fibrin glue contains a high fibrinogen concentration. As reported by Alston et al,[37] both tensile and adhesion strengths increased with increasing fibrinogen concentration; and these strengths were increased, as per our protocol of preparation, by the addition of calcium. They concluded that autologous fibrin glue had mechanical properties equivalent to those of the commercial product and was considered a good alternative.

Fibrin glue proved to enhance axonal elongation and was associated with an increase in regeneration distance and number of arborizing axons during early peripheral nerve regeneration.[38] This, in turn, might result in better functional and electrophysiological outcomes. However, our subgroup analysis revealed similar amplitude, latency, and duration of the cMUAP for the ulnar and median nerves in both the fibrin glue and microsuture groups. In contrast, Martins et al[39] demonstrated significantly better latency and conduction velocity of the cMUAP in the fibrin glue group 6 months postoperatively. The difference between the results of Martins et al[39] and our results could be due to different study designs; we were investigating humans, whereas they were investigating a rat model.

The aim of our hand therapy protocol was to activate the small hand muscles with electrical stimulation, because repetitive, task-specific movements using electrical stimulation can prevent disuse atrophy and contractures.[18] This protocol was applied to both groups 5 days/week over 6 weeks, because this was the recommended frequency of sessions in the literature.[18,19,40] We set the pulse frequency to 30 Hz, which is the normal recruitment rate of forearm muscles. Although greater muscle force may be enhanced by higher frequencies, the muscle tends to rapidly fatigue, reducing the total session duration.[18] Regarding our work-rest cycles, the ON time was set to 10 seconds and the OFF time to 30 seconds.[17] This longer rest time between contractions induced continued muscle tension during the session, whereas shorter rest times (5 seconds or 10 seconds) were associated with quick muscle fatigue leading to less voluntary muscle work.[18,41]

Autologous fibrin glue has no risk of transmission of viral infection or immunological reactions and is easily available, whereas commercial glues are prepared using a complex procedure that includes fibrinogen isolation from pooled human plasma and heat inactivation to minimize the risk of viral contamination.[42,43] Commercial glues are comparatively expensive and may not always be accessible on demand.[37]

The strengths of our study include the prospective comparison between 2 randomized groups, similar follow-up plans, objective outcome assessment, the autologous nature of the fibrin glue, and the fact that no patient was lost to follow-up.

The limitations include the relatively small sample size, lack of blinding, and short follow-up duration. However, motor recovery, if it happens, should be achieved during our follow-up period that extends up to 18 months; motor end plates usually atrophy 12−18 months after nerve injury.[19,24,44] Another limitation is the addition of secondary outcomes that were not pre-specified before trial initiation. However, this trial modification resulted from new information in the literature regarding the enhancement effect of fibrin glue on axonal elongation during early nerve regeneration and possible causes of faster recovery.[38] This, in turn, merits the addition of some secondary endpoints to make the study more informative. Although some would argue that drawing 1 unit of blood is a drawback of this study, any individual may safely donate 450 mL, especially given

that we strictly follow the European guidelines for donor selection, as previously described.[14]

In conclusion, although similar recovery of motor and sensory functions may be obtained after repairing peripheral nerves by either fibrin glue or conventional microsuturing, the use of autologous fibrin glue is safe and associated with shorter operative time.

REFERENCES

1. Cruz NI, Debs N, Fiol RE. Evaluation of fibrin glue in rat sciatic nerve repairs. *Plast Reconstr Surg*. 1986;78(3):369−373.
2. Maeda T, Hori S, Sasaki S, et al. Effects of tension at the site of coaptation on recovery of sciatic nerve function after neurorrhaphy: evaluation by walking-track measurement, electrophysiology, histomorphometry, and electron probe X-ray microanalysis. *Microsurgery*. 1999;19(4):200−207.
3. Kang JR, Zamorano DP, Gupta R. Limb salvage with major nerve injury: current management and future directions. *J Am Acad Orthop Surg*. 2011;19(suppl 1):S28−S34.
4. Ornelas L, Padilla L, Di Silvio M, et al. Fibrin glue: an alternative technique for nerve coaptation—Part I. Wave amplitude, conduction velocity, and plantar-length factors. *J Reconstr Microsurg*. 2006;22(2):119−122.
5. Ornelas L, Padilla L, Di Silvio M, et al. Fibrin glue: an alternative technique for nerve coaptation–part II. Nerve regeneration and histomorphometric assessment. *J Reconstr Microsurg*. 2006;22(2):123−128.
6. Becker CM, Gueuning CO, Graff GL. Sutures or fibrin glue for divided rat nerves: Schwann cell and muscle metabolism. *Microsurgery*. 1985;6(1):1−10.
7. Rafijah G, Bowen AJ, Dolores C, et al. The effects of adjuvant fibrin sealant on the surgical repair of segmental nerve defects in an animal model. *J Hand Surg Am*. 2013;38(5):847−855.
8. Atrah HI. Fibrin glue. *BMJ*. 1994;308(6934):933−934.
9. Spotnitz WD. Fibrin sealant: past, present, and future: a brief review. *World J Surg*. 2010;34(4):632−634.
10. Nishimura MT, Mazzer N, Barbieri CH, et al. Mechanical resistance of peripheral nerve repair with biological glue and with conventional suture at different postoperative times. *J Reconstr Microsurg*. 2008;24(5):327−332.
11. Choi BH, Han SG, Kim SH, et al. Autologous fibrin glue in peripheral nerve regeneration in vivo. *Microsurgery*. 2005;25(6):495−499.
12. de Medinaceli L, Prayon M, Merle M. Percentage of nerve injuries in which primary repair can be achieved by end-to-end approximation: review of 2,181 nerve lesions. *Microsurgery*. 1993;14(4):244−246.
13. Narakas A. The use of fibrin glue in repair of peripheral nerves. *Orthop Clin North Am*. 1988;19(1):187−199.
14. Keitel S. Guide to the Preparation, *Use and Quality Assurance of Blood Components. Principles of Autologous Transfusion*. 19th ed. European Directorate for the Quality of Medicines & HealthCare, Council of Europe; 2017.
15. Cavichiolo JB, Buschle M, Carvalho B. Comparison of fibrin adhesives prepared by 3 different methods. *Int Arch Otorhinolaryngol*. 2013;17(1):62−65.
16. De Somer F, De Brauwer V, Vandekerckhove M, et al. Can autologous thrombin with a rest fraction of ethanol be used safely for activation of concentrated autologous platelets applied on nerves? *Eur Spine J*. 2006;15(4):501−505.
17. Cauraugh J, Light K, Kim S, et al. Chronic motor dysfunction after stroke: recovering wrist and finger extension by electromyography-triggered neuromuscular stimulation. *Stroke*. 2000;31(6):1360−1364.
18. Nussbaum EL, Houghton P, Anthony J, et al. Neuromuscular electrical stimulation for treatment of muscle impairment: critical review and recommendations for clinical practice. *Physiother Can*. 2017;69(5):1−76.
19. Sallam AA, El-Deeb MS, Imam MA. Nerve transfer versus nerve graft for reconstruction of high ulnar nerve injuries. *J Hand Surg Am*. 2017;42(4):265−273.
20. Adams V. Electromyostimulation to fight atrophy and to build muscle: facts and numbers. *J Cachexia Sarcopenia Muscle*. 2018;9(4):631−634.
21. Brandsma JW, Schreuders TA. Sensible manual muscle strength testing to evaluate and monitor strength of the intrinsic muscles of the hand: a commentary. *J Hand Ther*. 2001;14(4):273−278.
22. Daniels L, Worthingham C. *Muscle Testing: Techniques of Manual Examination*. 5th ed. Saunders; 1986.
23. Jaquet JB, Luijsterburg AJ, Kalmijn S, et al. Median, ulnar, and combined median-ulnar nerve injuries: functional outcome and return to productivity. *J Trauma*. 2001;51(4):687−692.
24. Sallam AA, El-Deeb MS, Imam MA. Useful functional outcome can be achieved after motor nerve transfers in management of the paralytic hand. An observational study. *HSS J*. 2016;12(1):2−7.
25. Toreih AA, Sallam AA, Ibrahim CM, et al. Intercostal, ilioinguinal, and iliohypogastric nerve transfers for lower limb reinnervation after spinal cord injury: an anatomical feasibility and experimental study. *J Neurosurg Spine*. 2018;30(2):268−278.
26. Petersen P, Petrick M, Connor H, et al. Grip strength and hand dominance: challenging the 10% rule. *Am J Occup Ther*. 1989;43(7):444−447.
27. Chung KC, Pillsbury MS, Walters MR, et al. Reliability and validity testing of the Michigan Hand Outcomes Questionnaire. *J Hand Surg Am*. 1998;23(4):575−587.
28. Hweidi SA, Saied SM, Abulezz TA, et al. Comparison between conventional microsurgical technique and fibrin glue in repair of peripheral nerve injuries. *J Plast Reconstr Surg*. 2012;36(2):233−238.
29. Menovsky T, Beek JF. Laser, fibrin glue, or suture repair of peripheral nerves: a comparative functional, histological, and morphometric study in the rat sciatic nerve. *J Neurosurg*. 2001;95(4):694−699.
30. Moy OJ, Peimer CA, Koniuch MP, et al. Fibrin seal adhesive, versus nonabsorable microsuture in peripheral nerve repair. *J Hand Surg Am*. 1988;13(2):273−278.
31. Egloff DV, Narakas A. Nerve anastomoses with human fibrin. Preliminary clinical report (56 cases). *Ann Chir Main*. 1983;2(2):101−115.
32. Anani R, El-Sadek AN. Fibrin glue versus microsurgical sutures in peripheral nerve repair: experimental and clinical study. *J Plast Reconstr Surg*. 2009;33(1):69−74.
33. Boedts D. A comparative experimental study on nerve repair. *Arch Otorhinolaryngol*. 1987;244(1):1−6.
34. Temple CL, Ross DC, Dunning CE, et al. Resistance to disruption and gapping of peripheral nerve repairs: an in vitro biomechanical assessment of techniques. *J Reconstr Microsurg*. 2004;20(08):645−650.
35. Isaacs JE, McDaniel CO, Owen JR, et al. Comparative analysis of biomechanical performance of available "nerve glues. *J Hand Surg Am*. 2008;33(6):893−899.
36. Siqueira MG, Martins RS. Conventional strategies for nerve repair. In: Haastert-Talini K, Assmus H, Antoniadis G, eds. *Modern Concepts of Peripheral Nerve Repair*. Springer International Publishing; 2017:41−51.
37. Alston SM, Solen KA, Broderick AH, et al. New method to prepare autologous fibrin glue on demand. *Transl Res*. 2007;149(4):187−195.
38. Koulaxouzidis G, Reim G, Witzel C. Fibrin glue repair leads to enhanced axonal elongation during early peripheral nerve regeneration in an in vivo mouse model. *Neural Regen Res*. 2015;10(7):1166.
39. Martins RS, Siqueira MG, Silva CF, et al. Electrophysiologic assessment of regeneration in rat sciatic nerve repair using suture,

fibrin glue or a combination of both techniques. *Arq Neuropsiquiatr*. 2005;63(3a):601–604.
40. Rosewilliam S, Malhotra S, Roffe C, et al. Can surface neuromuscular electrical stimulation of the wrist and hand combined with routine therapy facilitate recovery of arm function in patients with stroke? *Arch Phys Med Rehabil*. 2012;93(10):1715–1721.e1.
41. Newsam CJ, Baker LL. Effect of an electric stimulation facilitation program on quadriceps motor unit recruitment after stroke. *Arch Phys Med Rehabil*. 2004;85(12):2040–2045.
42. Piccin A, Di Pierro AM, Canzian L, et al. Platelet gel: a new therapeutic tool with great potential. *Blood Transfus*. 2017;15(4):333.
43. Bojanic I, Mravak Stipetic M, Pulanic D, et al. Autologous blood as a source of platelet gel for the effective and safe treatment of oral chronic graft-versus-host disease. *Transfusion*. 2018;58(6):1494–1499.
44. Grinsell D, Keating CP. Peripheral nerve reconstruction after injury: a review of clinical and experimental therapies. *Biomed Res Int*. 2014. 2014:698256.