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Fibrin Glue Versus Microsurgical Sutures in Peripheral Nerve Repair: Experimental and Clinical Study

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ABSTRACT

Currently, microsutures and fibrin glue are the commonly used techniques in peripheral nerve repair with controversies in the results of experimental researches studying both techniques. This experimental and clinical randomized prospective trial aimed at evaluation of the efficiency of fibrin glue compared with microsuturing technique in peripheral nerve repair. Twenty male Wistar rats were used in the experimental part of the study. In each rat, the sciatic nerve on both sides was transected and repaired by microsutures on one side and fibrin glue on the other side. Twelve weeks after repair, neither neuroma nor dehiscence was found in any nerve repaired by either technique. Histological comparison showed no statistically significant difference between both techniques regarding the count of regenerated axons distal to the site of nerve repair. The clinical part of the study included 20 patients suffering from acute median nerve injury in the distal part of the forearm. They were divided randomly into 2 groups, one repaired with microsutures and the other by fibrin glue. The mean operative time of nerve repair was significantly shorter in the group repaired by fibrin glue but with higher costs compared to the other group. Sex months after repair, the sensory and motor (EMG) grading of patients of both groups showed no statistically significant difference. Fibrin glue and microsutures are equal regarding maintenance of integrity of nerve after repair and have the same outcome of nerve regeneration. Fibrin glue can be a good alternative for peripheral nerve repair in selected cases. It can be used efficiently in cases of multiple peripheral nerve injuries, in cases that need multiple cable nerve grafts and moreover in situations where suture application is difficult or impossible for technical reasons.

INTRODUCTION

Peripheral nerve injury and repair remains a challenge for surgeons. An ideal nerve repair would be relatively non-traumatic to the already injured tissues, eliminate foreign body reaction and allow prompt restoration of the normal endoneurial environment. It is equally important that the technique would permit easy and efficient use in the clinical setting [1].

At the present time, accurate approximation of nerve ends, using microsurgical sutures, remains the gold standard technique. This conventional technique has, however, a number of inherent problems. The process of suture placement requires multiple passages of the needle through the friable epineurium that inevitably lead to trauma and structural disturbance. The presence of non-absorbable suture material leads to a foreign body reaction with subsequent granuloma and scar formation. Also, sutures are placed only periodically within the epineurium and gaps remain that permit the invasion of inflammatory cells and the escape of mediators essential for nerve regeneration [2]. These problems have prompted investigators to seek alternative methods for coapting severed nerves. Recently, attention has been paid to non-suture techniques especially fibrin glue as a means of eliminating sutures from the repair site [2-10].

The purpose of this study was to evaluate experimentally and clinically, the efficiency of fibrin glue compared with microsuturing technique in peripheral nerve repair.

MATERIAL AND METHODS

A- *Experimental study:*

The Ethical review Committee of Faculty of Medicine, Zagazig University, Zagazig, Egypt approved the experiment. Twenty male Wistar rats weighing between 250 and 300 grams were used in our study. All animals were anesthetized with intraperitoneal sodium pentothal in a dose of 0.04mg/g body weight. The dorsal aspect of both rat hind limbs till the midback was prepared by shaving and bovidone iodine washing. The animal was put in prone position and fixed on a rodent operating board. Using the operating microscope, the sciatic nerve on both sides was exposed through a dorsolateral incision in the thigh (Fig. 1). Bilateral sciatic nerve transection was done by a sharp blade (Fig. 2). On the right side, the nerve was repaired with 4 epineurial microsutures using 10/0 Polyamide 6 (Ethilon®; Ethicon, U.K.) (Fig. 3). On the left side, the transected nerve was glued with fibrin glue (Tisseel kit®; Baxter, Vienna, Austria). Fibrin glue was applied to the epineurium of the proximal and distal stumps of the nerve (Fig. 4). Care was taken that a maximum contact area between nerve ends was obtained and the stumps were accurately coapted. The glue was applied as a cuff and not to the section surface. Stabilization of the nerve ends was maintained for 2 minutes. Wound was washed with saline and skin closed with 2-0 silk sutures. The rats were housed in separate cages following the guidelines of the animal house of Faculty of Medicine, Zagazig University. Each of them had its individual source of water and standard rat food.

Twelve weeks after surgery, the animals were anesthetized and the repaired nerves were exposed in the same manner as described for the first surgery. Gross appearance of nerves was observed for any dehiscence or neuroma formation. Nerves were then harvested bilaterally. A 15-mm segment was excised distal to and including the anastomotic site. The animals were sacrificed with an overdose of sodium pentothal injected intraperitoneally. Sections were obtained from the distal part of the nerve, close to the transection region. The specimens were fixed in 10% glutaraldehyde solution and stained with toluidine blue. Cross-sectional preparations were examined by light microscopy under x400 magnification. A count was made for the regenerated myelinated axons (Fig. 5 A,B). The mean axon count of each specimen was the mean count of the microscopic fields of 4 sections of each nerve. The difference in the mean axon count between the nerves repaired with fibrin glue technique and that repaired with microsuture technique was analyzed with the paired *t* test. *p* value less than 0.05 was considered significant.

B- *Clinical study:*

A total of 20 patients presented with acute low median nerve injury were included in this study. All of them were males with their ages ranged between10-34 (Mean 20.7±6.3 years). Both groups were homogeneous regarding the age (Table 4). All patients underwent surgical treatment at the Department of Surgery, Zagazig university hospitals. The patients were divided equally into two groups; group (A), 10 patients subjected to fibrin glue as a mean of peripheral nerve repair and group (B), 10 patients subjected to microsurgical suturing technique.

Operative technique:

Under general anesthesia and tourniquet control, adequate exposure of the median nerve was obtained by dissecting it from the surrounding tissue under magnification, maintaining the integrity of the mesoneurium and the nerve. The interfascicular blood clot was removed in order not to obstruct alignment. Initially, if needed, trimming the nerve ends was done to remove dead or severely damaged tissue by a single clean stroke with a No. 11 scalpel blade against a firm background (a sterile moistened tongue blade). Then, trial at approximation of both ends was attempted to gauge the amount of tension necessary, which is related to the length of the gap between the stumps. To achieve a tension free repair, some flexion of the wrist joint was done to decrease the tension on the repair. If the gap between the cut ends was wide, nerve graft was needed and the patient was excluded from this study. Coaptation of the nerve stumps was performed, which described the apposition of corresponding nerve ends with special attention to bringing fascicles into optimal contact. Longitudinal blood vessel running on the median nerve was used as a key for nerve alignment to avoid malorientation during repair. Lastly, maintenance of coaptation was achieved with the use of fibrin glue (Tisseel kit®; Baxter, Vienna, Austria) in group (A) of patients and 9/0 Polyamide 6 (Ethilon®; Ethicon, U.K.) epineurial microsutures in group (B) (Figs. 6,7). Hemostasis was achieved in all wounds after the tourniquet was let down and before skin closure. The extremity was splinted in a position placing the least amount of tension on the nerve repair. Immobilization in dynamic splint was done for 3 weeks. The operative time and costs for nerve anastomosis were assessed in both groups.

Follow-up:

All patients were subjected monthly to neurologic sensory evaluation to the median nerve zone in the hand and Electromyography (EMG) to abductor policis brevis muscle. By the end of the 6th month after surgery, final sensory and EMG grading was done as shown in Tables (1,2).

Statistical analysis:

Student *t* test was used for comparing the 2 groups regarding age, operative time and costs. Sensory and EMG grading of both groups were compared using Fisher's Exact Test. *p* Values less than 0.05 were considered significant.

RESULTS

Experimental study:

Animal loss: Seven rats died in the postoperative period. On final assessment, 13 rats were available.

Histopathologic study:

Gross appearance of the repair: Under the microscope, neither anastomotic rupture nor neuroma was noticed in any of the nerves repaired by both techniques.

Quantitative evaluation: Comparing the mean count of myelinated axons in the distal segments of nerves, there was no statistically significant difference between the nerves repaired by either technique (Table 3).

Clinical study:

There was significant difference between both groups concerning the operative time in favor of fibrin glue group but with significantly higher cost. The sensory and EMG grading of patients of both groups showed no statistically significant difference (Table 4).

Fig. (1): The sciatic nerve of the rat exposed under the microscope.

Fig. (2): The nerve transected.

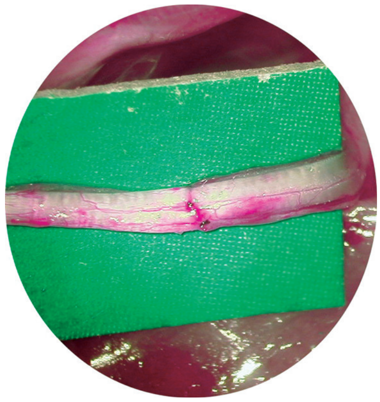

Fig. (3): The nerve repaired by 10/0 Ethilon microsutures.

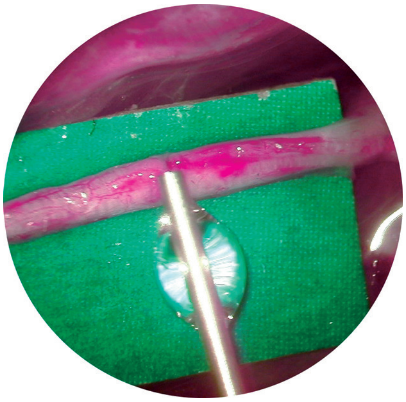

Fig. (4): Application of the fibrin glue for repair the nerve.

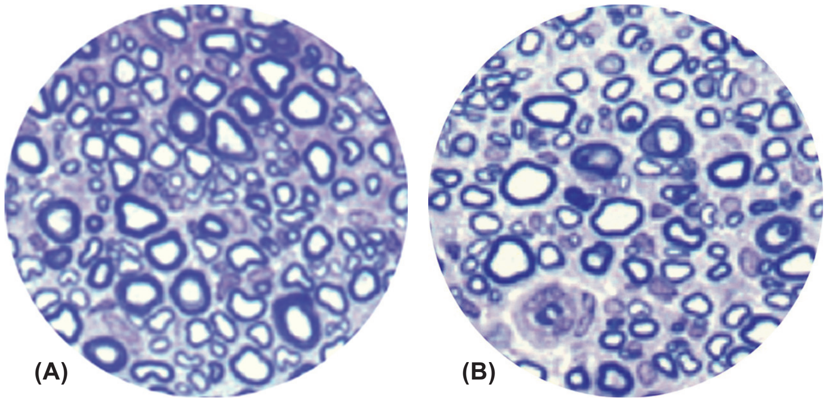

Fig. (5): Photomicrograph, showing the density of myelinated nerve fibers in the cross-section of the nerve segment distal to the repair by fibrin glue (a) and microsuture (b) techniques in rats examined 12 weeks after repair (X400, Toludine blue stain).

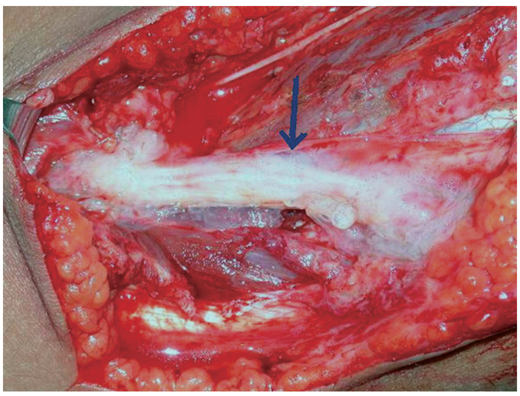

Fig. (6): Median nerve repaired by fibrin glue (arrow).

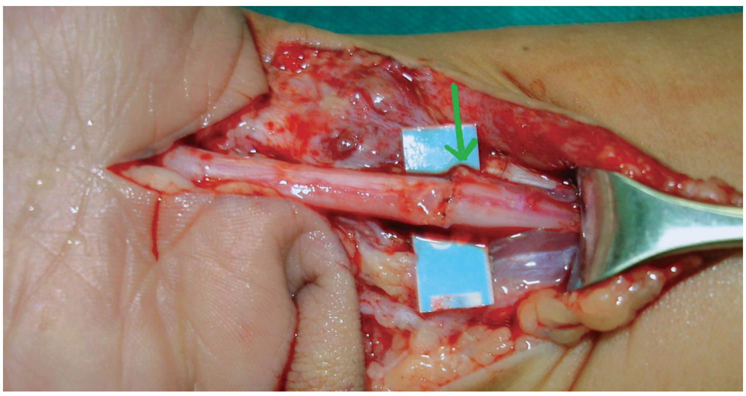

Fig. (7): Median nerve repaired by microsutures (arrow).

Table (1): Medical research council system for grading of nerve sensory recovery [11].

S1	Recovery of deep cutaneous pain
S1+	Recovery of superficial pain
S2	Recovery of superficial pain and some touch
S2+	As in S2, but with over response
S3	Recovery of pain and touch sensibility with disappearance of over response
S3+	As in S3, but localization of the stimulus is good and there is imperfect recovery of 2-point discrimination
S4	Complete recovery

Table (2): Electromyography (EMG) grading scale of nerve motor recovery [12].

E0	Total axonal degeneration
E1	Partial axonal degeneration
E1+	Partial axonal degeneration with regeneration
E2	Full recovery

Table (3): Count of myelinated axons in the nerve segment distal to the repair by fibrin glue and microsuture techniques in rats examined 12 weeks after repair.

Axon count	Fibrin glue	Microsuture	*p*
Range	22-35	21-33	
Mean±SD	28.15±2.23	27.53±4.17	0.647

Table (4): Patients data of both groups.

Data	Fibrin glue group	Suture group	*p*
Age in years:			
Range	10-25	10-34	
Mean±SD	20.1±4.38	21.3±7.98	0.682
Operative time of nerve repair (in minutes):			
Range	2-5	22-35	
Mean±SD	3.5±1.08	28.8±4.68	<0.001
Costs of one nerve repair in L.E.:			
Range	800	244-270	
Mean±SD		257.7±9.43	<0.001
Sensory scale:			
S3+	3	4	
S4	7	6	1.0
EMG scale:			
E1+	5	4	
E2	5	6	1.0

DISCUSSION

In peripheral nerve microsurgery, accurate adaptation and apositioning of the different fascicles is important. Epineurial, perineurial and interfascicular techniques have been advocated. Microsurgical magnification and more precise knowledge of anatomy have improved the results [13]. Studies in the rats have demonstrated that the number of regenerated axons do not differ after perineurial or epineurial nerve repair [14]. Suture placement has been thought to cause a hindrance to the sprouting axons and compress the blood supply to the fascicles, thereby impairing the regeneration of the transected nerve ends after repair [15]. Moreover, formation of suture granuloma obstructs myelin and axonal regeneration. These factors led to the development of various tissue sealants for the purpose of atraumatic tissue repair. Among these materials is fibrin glue [7-9], Cyanoacrylate [10], photochemical tissue bonding [2] of them, only fibrin glue is the natural material. Hypothetically, fibrin glue repair technique itself may have its own disadvantages, such as penetration of the adhesive through the suture line and pronounced connective tissue reaction induced by glue, causing nerve compression. However, Palazzi et al. [16] demonstrated that fibrin glue is a sealant and not a nerve barrier. There is no appreciable clot retraction because the sealant does not contain thrombocytes.

In the experimental part of our study, neither anastomotic dehiscence nor neuroma formation has been found in any of the nerves repaired by either technique. This has been also reported in the literature [3,7,8,9]. However, Wieken et al. [4] stated that a tension-free repair is necessary with the use of glue but that gapping may occur, limiting the use of the agent in promoting reneurotization. We agree with them that tension free repair is a fundamental factor in preventing dehiscence in any technique used for nerve repair. Choi et al. [17] reported that stitches may shift toward the center of the cross-section and cause a foreign-body reaction. We believe that this might be true if sutures were put under tension.

Previous experimental results on neural anastomosis using fibrin glue have tended to be less than satisfactory, as it does not have sufficient tensile strength to hold a peripheral nerve repair and moreover, it produces stricture at the anastomosis site [18,19]. However, our study did not show any case of anastomosis failure by the end of the follow-up period.

Other reports [3,10] found that 90 days are enough to asses the regeneration in transected nerve in the rat. By this time, myelinated nerve fibers are well formed distal to the anastomosis. So, we did our histological examination of the nerves 12 weeks after repair. To compare the regeneration of sciatic nerves in rats repaired by the two techniques, we used a simple quantitative measure, the number of regenerated myelinated axons. We found it easy and it does not require sophisticated methods used by others [4,5,10]. In the present study, histologic evaluation showed good axonal regeneration across the anastomotic site with no difference in the outcome of nerve regeneration between suture and fibrin glue repair. This was also confirmed by other investigators [3,7]. However, Junior et al. [5] found less count of regenerated axons in nerves repaired by fibrin glue compared to epineurial sutures without significant difference in EMG results. Jubran and Widenfalk [20] found that fibrin glue containing nerve growth factor (NGF) and glial cell line-derived neurotrophic factor (GDNF) has beneficial effect on nerve regeneration either alone or in combination with microsutures. This may open the horizon in the future for use of these materials in the clinical practice.

In the clinical part of the study, we chose the distal part of the median nerve to be the site of our study. At this level, the nerve is nearly purely sensory. The 3 thenar muscles (abductor pollicis brevis, flexor pollicis brevis, opponens pollicis) and 2 radial lumbrical muscles are supplied by the nerve distal to the level of injury. So, the motor function of the regenerated nerve can be assessed by EMG of the abductor policis muscle [12]. On assessment of the recovery of sensory function of the nerve, we followed the grading system of the medical research council system for grading nerve recovery [11]. We found no similar study in the literature comparing the fibrin glue with microsutures using the isolated median nerve at this level as the area of study.

Our study showed no statistically significant difference between both groups regarding the sensory and motor recovery of the nerve. This means that whatever the method used for nerve coaptation, the results will be satisfactory as long as the rules of nerve repair are followed. Good orientation of both nerve ends using the vasa nervosa running on the surface of the nerve as a key for orientation, good trimming of the unhealthy nerve ends, removal of any interfascicular blood clots, gentle nerve handling and repair without any tension together with postoperative splinting and immobilization for sufficient time are the crucial factors in obtaining satisfactory results in nerve repair rather than the method of repair [11,21,22].

In the view of the similar results of both techniques, the crucial factor in the choice of either of them will be the operative time and costs. In our study, the spent time of nerve repair using fibrin glue was significantly lower than that of microsuture technique. However, the costs were significantly higher. If we knew that one package of 1ml fibrin glue will be sufficient for repair of 3 nerves, then, it will be much less costly and much more time saving than microsuture technique in repair of multiple nerve injuries. Another clinical situation that will make the fibrin glue more favorable is the need of multiple cable nerve grafts for nerve repair as in cases of brachial plexus injuries and late secondary repair of major peripheral nerve injuries [23]. Microsutures will be much more difficult in nerve orientation, will take much more operative time and consequently more costs. In some clinical situations, microsutures are difficult or impossible to apply as in cases of brachial plexus injuries with short root stumps or facial nerve injuries on coming out from the stylomastoid foramen. Here, fibrin glue will be the only feasible mean for nerve coaptation.

Conclusion:

Based on the results of this study, we can conclude that fibrin glue and microsuturing techniques are equally adequate to maintain the continuity of repaired peripheral nerves, have similar outcome of nerve regeneration and have the same results of sensory and motor recovery. In the view of easy application, shorter operative time but higher costs of fibrin glue compared to conventional microsutures, we suggest its use in multiple peripheral nerve injuries, secondary nerve repair with the need to multiple cable grafts and in situations where suture application is difficult or impossible for technical reasons.

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