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Comparison of a new single-donor human fibrin adhesive with suture for posterior tibial nerve repair in rat: biomechanical resistance and functional analysis

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【**Abstract**】**Objective:** The use of fibrin adhesives has a broad background in nerve repair. Currently the suboptimal physical properties of single-donor fibrin adhesives have restricted their usage. The present experiment studies the performance and physical characteristics of a modified fibrin glue prepared from single-donor human plasma in the repair of posterior tibial nerve of rat.

Methods: Forty Wistar rats were divided into 5 groups; in the control group, tibial nerve was completely transected and no treatment was done, while in the four experimental groups the nerve stumps were reconnected by one suture, three sutures, one suture with fibrin glue and fibrin glue alone respectively. During 8 weeks of follow-up, Tibial Function Index was measured weekly and adhesive strength, inflammation and scar formation were assessed at the end of the study.

Results: Nerve stumps dehiscence rate and adhesive strength were similar in all experimental groups and significantly differed from control group (P<0.05). By the end of the eighth follow-up week, functional recovery of one and three sutures groups were significantly higher than groups in which fibrin glue was used for repair (P<0.05). The amount of inflammation and scar tissue formation was similar among all groups.

Conclusion: The study results show that the prepared single-donor fibrin adhesive has acceptable mechanical properties which could provide required adhesiveness and hold nerve stumps in the long term; yet, we acknowledge that more studies are needed to improve functional outcome of single donor fibrin adhesive repair.

Key words: ***Rats; Nerve regeneration; Fibrin tissue adhesive; Materials testing***

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Peripheral nerve injuries are among the most prevalent and disabling clinical conditions.[1] Better understanding of the nerve ultrastructure and advancement in microsurgical techniques have made microsuturing the most widely used therapeutic strategy for nerve repair.[2] However, conventional nerve suturing is technically demanding and time consuming, and may cause traumatic and inflammatory injuries to the nerve stumps, leading to unpredictable and suboptimal outcomes in some cases.[3,4] For these reasons the translational researches for developing alternative nerve neurorrhaphy techniques have been considered over the last several decades.

The use of fibrin glue in peripheral nerve repair is among the first successful applications of alternative nerve neurorrhaphy techniques, and currently, it is a popular alternative for suturing.[5] In 1940, Young et al[6] used the human fibrinogen for repairing the peripheral nerves, first in animal models and then in clinics. In 1983 Egloff and Narakas[7] extensively

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documented the performance of this adhesive on 56 patients. Subsequent studies showed inconsistent efficacy of this adhesive in nerve repair.[8,9]

Fibrin adhesives can be made from human or bovine, pooled or single-donor plasma. Noncommercial adhesive plasma is usually obtained from a single donor and thus called autologous, while commercial adhesives or pooled adhesives are made from a pool of plasma units of hundreds of donors and have higher fibrinogen concentration which provide greater adhesion force[10-13]; yet, a major drawback of using a multiple-donor source is the risk of viral infection even after virus elimination process. The risk is almost absent in single-donor fibrin adhesives.[14]

For decades, poor adherence and tensile strength have been the main problem with fibrin adhesives. However, modified preparation methods have improved their mechanical properties, resulting in increased usage.[15,16]

Subsequent animal studies have shown the advantages of pooled fibrin glue over sutures.[4,9,17,18] However, poor mechanical resistance of single-donor type, due to lower fibrinogen concentration, has restricted its usage.[8,19-21]

Nishimura et al[15] have compared the mechanical properties of commercial fibrin adhesive against sutures at different postoperative temporal milestones. They have shown that the mechanical properties of sutures are superior to those of the commercial fibrin adhesive immediately and seven days after repair. However, they manifest the same mechanical properties four weeks after operation. The commercial fibrin adhesives contain aprotinin which is an antifibrinolytic agent. Aprotinin prevents the premature fibrinolysis of adhesives; therefore, it prolongs the life span of the adhesive in the plasmin-rich environment in vivo. Further studies on single-donor fibrin adhesives, which are usually depleted from aprotinin, are yet to be done in order to reach acceptable adhesive capacity to maintain nerve integrity throughout the healing period.

The present study was conducted to compare functional and biomechanical efficacy of a single-donor fibrin adhesive in vivo with conventional microsuturing in repair of posterior tibial nerve cuts in rats.

METHODS

Study design

Our study was conducted according to Tehran University Ethical Committee Guidelines. Forty male Wistar rats were divided into five groups. In group A (control group), tibial nerve was completely transected and no treatment was done. In experimental groups B, C, D and E, the nerve stumps were reconnected by one suture, three sutures, one suture with fibrin glue, and fibrin glue alone respectively. Weekly behavioral evaluations were conducted for two months to compare how much the severed nerve functions were restored. At the end of the study, macroscopic and microscopic evaluations were performed as well as adhesive strength quantification at site of injury.

Fibrin adhesive preparation

One unit of fresh frozen plasma was obtained from the Blood Transfusion Organization. Fibrin adhesive was prepared by modified Yoshida technique as follows[22]: followed by adding ethanol, fibrinogen was precipitated at a temperature of 0°C for 1 hour. The sediment was extracted and dissolved by an equal amount of blood plasma. The mixture was kept at 37°C for 8 minutes to ensure complete evaporation of the ethanol component. The soluble fibrin was drawn into a separate syringe and stored at -20°C until the day of surgery.

The Saxena method[23] was used to prepare thrombin. Thrombin was precipitated by reducing acidity and osmolarity; the sediment was dissolved in normal saline and calcium chloride was added to the solution. The thrombin solution was drawn into the separate syringe and kept at -20°C until the day of surgery.

Fibrinogen measurement

Plasma fibrinogen concentration was measured by the pathology laboratory. The fibrinogen concentration of the prepared solution was measured by Ingram method[24]. Briefly, after dilution, the fibrinogen was coagulated by adding thrombin. The excess fluid, eliminated by pressing the resulted