Nerve Glue for Upper Extremity Reconstruction

Raymond Tse, MD[a,b,*], Jason H. Ko, MD[c]

KEYWORDS

• Peripheral nerve • Nerve glue • Nerve adhesive • Nerve reconstruction

KEY POINTS

- Nerve glue is an attractive alternative to sutures to improve the results of nerve repair.
- Improved axon alignment, reduced scar and inflammation, greater and faster reinnervation, and better functional results have been reported with the use of nerve glue.
- The current formulations of fibrin glue are routinely used for nerve grafts and transfers and may have a role in augmenting suture repairs. Polyethylene glycol sealants are currently being studied for their suitability as nerve glue.

INTRODUCTION

> *In the hand sensation is equal in value to motion.*
>
> —*Sterling Bunnell, 1946*[1]

Although great strides to produce consistently favorable outcomes in hand surgery have been made, peripheral nerve reconstruction remains a challenge. Patient and disease factors may account for much of the variability in functional results; however, the effectiveness of nerve repair for end target reinnervation underlies any functional result. Nerve glue for nerve repair is an attractive alternative to the current standard suture repair. Advantages of an adhesive for nerve repair include ease of use, less tissue trauma, maintenance of nerve architecture, and better fascicular alignment. Although the ideal nerve glue is not yet available, progress continues toward this end.

PROPERTIES OF THE IDEAL NERVE GLUE

"Glue" is a liquid or semiliquid substance that tightly adheres items together. In the setting of human peripheral nerve repair, the ideal glue should have specific biologic, mechanical, and technical properties as outlined in **Table 1**. Safety requires that the substance have minimal risk of disease transmission, antigenicity, or toxicity. The glue should not induce fibrosis that can lead to nerve compression and in the case of substance interposition between nerves, it should not act as a barrier to nerve regeneration. Application of the glue should preserve the normal nerve architecture and should facilitate ideal fascicular alignment. The glue should provide adequate mechanical strength to prevent gapping or rupture at the initial repair and during the postoperative period. It should be easy to use with minimal equipment and easy to apply thereby reducing operative time. Finally, the glue should be versatile

The authors have identified no professional or financial affiliations for themselves or their spouse/partner.
[a] Division of Plastic Surgery, Department of Surgery, University of Washington, WA 98105, USA; [b] Brachial Plexus Program, Pediatric Plastic Surgery, Seattle Children's Hospital, 4800 Sand Point Way Northeast, M/S W-7847, Seattle, WA 98105, USA; [c] Hand and Microvascular Surgery, Department of Orthopaedics and Sports Medicine, University of Washington, Seattle, WA 98105, USA
* Corresponding author. Pediatric Plastic Surgery, Seattle Children's Hospital, 4800 Sand Point Way Northeast, M/S W-7847, Seattle, WA 98105.
E-mail address: raymond.tse@seattlechildrens.org

Hand Clin 28 (2012) 529–540
http://dx.doi.org/10.1016/j.hcl.2012.08.006
0749-0712/12/$ – see front matter

Table 1
Properties of the ideal nerve glue

	Biologic	Mechanical	Technical
Safety	No disease transmission No antigenic potential Nontoxic	Maintains tensile strength over time	No external energy sources for activation
Effectiveness and efficacy	Facilitates axon regeneration across coaptation Induces minimal or no inflammation or fibrosis	Facilitates fascicular alignment Maintains normal nerve architecture	Readily available Easy to use Reduces surgical time Versatile for different nerve repair scenarios

enough to be used in different clinical scenarios including primary nerve repair; nerve transfer (with single or multiple nerve elements); and nerve grafting (with single or multiple nerve elements).

DEVELOPMENT OF NERVE GLUE

Efforts to adhere nerves without suture date back to the 1940s when fibrin and clots were used for nerve coaptation.[2,3] Rapid absorption and low tensile strength produced disappointing results and efforts were not revived until the 1970s. Matras and coworkers[4,5] used a higher concentration of fibrinogen, factor XIII, calcium hydrochloride, and bovine thrombin to yield a longer lasting adhesive. Animal model studies demonstrated results similar to suture repair thereby prompting experimentation and development of nerve glues during the next several decades. Studies have examined various fibrin adhesives, platelet-rich plasma, cyanoacrylate, and laser solder welding. Because of ease of use, availability, and favorable results, fibrin sealants have been clinically used as nerve glue. The most recent candidate to be used as nerve glue is polyethylene glycol (PEG) hydrogel.

The different nerve glues are reviewed and evidence for or against their use is discussed with respect to the model used (animal, cadaver, or human) and the outcomes measured (biomechanics, histology, electrophysiology, and function). When interpreting results of animal and cadaver studies, it is important to recognize that clinical outcomes may not directly correlate. Currently, there are no commercially available products approved for use as nerve glue and any use is considered off-label.

FIBRIN GLUE

Fibrin is an end product of the coagulation cascade and building block of the hemostatic plug. The intrinsic and extrinsic coagulation pathways activate thrombin, which in turn cleaves fibrinogen to the fibrin monomers that polymerize to form a matrix. Factor XIII is also activated by thrombin and acts to covalently cross-link fibrin to form a stable clot.

The common components of fibrin sealants include fibrinogen, thrombin, and calcium chloride. Higher concentrations of fibrinogen increase strength, whereas higher concentrations of thrombin increase the rate of fibrinogen conversion. The addition of an antifibrinolytic can increase duration and addition of factor XIII may improve strength. Protein components can be human, bovine, or a combination and the antifibrinolytic agent is bovine or synthetic. When interpreting the results of studies using fibrin glue for nerve repair the formulation of the fibrin needs to be considered because the results may vary with different formulations.

Autologous fibrin glue has been produced by centrifuge and precipitation of fibrinogen from blood. When thrombin has been added to preparations, it is often from a bovine source because thrombin is not easily isolated. Production of truly autologous fibrin glue is limited by the need to add other components and the concentration of fibrinogen that can be made available is limited by the volume of plasma collected.

Generally, higher concentrations of fibrinogen are produced with commercially available fibrin sealants. **Table 2** summarizes the available products. Common to all of these products are concentrated fibrinogen and thrombin from a pooled human source that is treated with heat, detergent or solvent, and filtration to reduce the risks of disease transmission. The main distinguishing features are the antifibrinolytic agent or process. Tisseel (marketed as Tissucol in Europe) (Baxter, Westlake Village, CA) uses aprotinin that was previously of a bovine source but is now synthetic. Beriplast (CSL Behring, Kansas City, MO)