A systematic review and meta-analysis on the use of fibrin glue in peripheral nerve repair: Can we just glue it?

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Received 23 July 2021; accepted 8 January 2022

Abstract Background: Within the field of peripheral nerve surgery, the use of fibrin glue as an alternative to conventional microsurgical suture repair is becoming increasingly popular. Advantages of fibrin glue for nerve reconstruction include technical ease of use, less tissue manipulation, and shorter operation times. Although fibrin glue seems a promising alternative to conventional microsurgical repair, further insight into the outcomes of nerve recovery is essential.

Objective: To summarize the current literature on the use of fibrin glue for peripheral nerve repair and compare these results with outcomes following conventional suture repair.

Methods: A systematic search in Embase, MEDLINE, Web of Science, Cochrane, and Google Scholar databases was performed. The search included animal, cadaveric, and human studies assessing outcomes following peripheral nerve repair using fibrin glue. Data on outcomes were subdivided into functional outcomes, electrophysiology, histopathology, biomechanical outcomes, and operation times. We calculated standardized mean differences and combined these in a random effects model to estimate the overall effect.

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Results: From a total of 2057 references, 37 animal, two cadaveric, and four human studies were included. Fibrin glue repairs resulted in similar functional and electrophysiology outcomes and shorter operation times than suture repairs. However, fibrin glue alone resulted in lower strength and more dehiscence. No dehiscence was reported when fibrin glue was combined with one or two sutures. Yet, we also found that methodological details were poorly reported in animal studies, resulting in an unclear risk of bias. This should be taken into consideration when interpreting the results.

Conclusion: The results indicate that nerve regeneration may be similar in fibrin glue repairs and suture repairs. Combining fibrin glue with one or two positional sutures allows for a precise realignment of the nerve fibers and seems to provide sufficient strength to prevent dehiscence.

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Introduction

Following peripheral nerve injury, microsurgical suture repair is considered the gold standard for nerve coaptation. The most important advantage of suture repairs is the ability to perform a precise coaptation. Furthermore, sutures preserve tensile strength diminishing the risk of dehiscence.1,3 Yet, the microsurgical repair is a time-consuming and technically demanding procedure in cases with difficult exposure or small caliber nerves.1,4 In addition, the suture material may cause tissue reactions, including inflammation and scar formation, which may negatively impact nerve regeneration.1,4

A sutureless coaptation with tissue adhesives, such as fibrin glue, could overcome the disadvantages of conventional suture repair. Attempts to use fibrin glue for coaptation of peripheral nerves were first described in the literature in the 1940s.10,11 However, its application in clinical practice remained limited until the introduction of commercially available fibrin glue in the 1970s. Fibrin glues act as hemostatic agents. The main components include fibrinogen and thrombin derived from human or bovine blood, but most sealants contain two additional components; factor XIII and aprotinin. An overview of commercially available fibrin glues and their compositions is provided in Table 1. The combination of these active components promotes the formation of a fibrin clot by stimulating the final stage of the coagulation cascade.12,14 When applied to a nerve reconstruction, the fibrin clot forms an adhesive layer around the reconstruction site.13 Advantages of fibrin glue for nerve
reconstruction include technical ease of use, less tissue manipulation, and decreased operation times.\(^4\) Furthermore, fibrin glue could be beneficial in terms of inflammation and fibrosis.\(^5,15,16\)

Although fibrin glue is clinically used by many due to ease of use and promising results, its use for peripheral nerve repair is still considered off-label. This is mainly due to the lack of well-controlled large studies, as most studies are conducted on animals with small sample sizes and various outcome measures, which often impedes direct comparisons. Ten years ago, a systematic review compared outcomes of fibrin glue and suture repairs and concluded that fibrin glue is an excellent alternative to microsurgical repair for peripheral nerve injuries.\(^17\) Of the sixteen included studies, however, only one comprised human subjects and few evaluated measures of functional nerve regeneration. In addition, a limited number of studies specifically evaluated a combination of sutures and fibrin glue. Hence, the question remains if fibrin glue should be combined with a reduced number of positional sutures to strengthen the reconstruction. In the past decade, there has been a substantial increase in the number of studies on this topic. Therefore, this systematic review and meta-analysis aimed to summarize the available literature on the use of fibrin glue for peripheral nerve repair and compare these results with outcomes following conventional microsurgical repair. The specific review questions that were addressed are as follows: (1) Does the use of fibrin glue for the repair of peripheral nerve injury result in similar nerve regeneration compared to conventional suture repair?; and (2) Does the use of fibrin glue alone yield sufficient strength for coaptation or is an additional suture required for strengthening of the coaptation?

**Methods**

**Protocol and registration**

This systematic review protocol was specified before conducting the study and registered in an international database (PROSPERO, registration number CRD42021246252).

**Eligibility criteria**

Studies were included if they met the following criteria: (1) a population consisting of animal, cadaveric, or human subjects with peripheral nerve injury; (2) reconstruction

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**Table 1** Overview of commercially available liquid fibrin glue agents and their composition.

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
<th>Active ingredients (per mL)</th>
<th>Available dosages</th>
<th>Relative costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artiss</td>
<td>Baxter</td>
<td>Human fibrinogen (91 mg), factor XIII (0.6–5 IE), thrombin (4 IU), synthetic aprotinin (3000 KIU)</td>
<td>2, 4, and 10 mL</td>
<td>$</td>
</tr>
<tr>
<td>Beriplast</td>
<td>CSL Behring</td>
<td>Human fibrinogen (90 mg), factor XIII (60 IU), thrombin (500 IU), bovine aprotinin (1000 KIU)</td>
<td>0.5, 1, and 3 mL</td>
<td>$$</td>
</tr>
<tr>
<td>Evicel</td>
<td>Ethicon</td>
<td>Human fibrinogen (70 mg), thrombin (1000 IU)</td>
<td>2, 4, and 10 mL</td>
<td>$$</td>
</tr>
<tr>
<td>Fitrix</td>
<td>Sanquin</td>
<td>Human fibrinogen (15 mg), fibrinectin (8 mg), factor XIII (3 IU), factor VIII (16 IU), von Willebrand factor (25 IU), plasminogen (2 IU), thrombin (30 IU)</td>
<td>1, 2, and 5 mL</td>
<td>Not available</td>
</tr>
<tr>
<td>Hemaseel</td>
<td>Haemucure Corp.</td>
<td>Human fibrinogen (91 mg), thrombin (500 IU), aprotinin (3000 KIU)</td>
<td>1, 2, and 5 mL</td>
<td>Not available</td>
</tr>
<tr>
<td>Quixil / Crosseal</td>
<td>Omrix Biopharmaceuticals</td>
<td>Human fibrinogen and fibrinectin (70 mg), thrombin (1000 IU), bovine tranexamic acid (95 mg)</td>
<td>1, 2, and 5 mL</td>
<td>$$</td>
</tr>
<tr>
<td>Tissucol / Tisseel</td>
<td>Baxter</td>
<td>Human fibrinogen and fibrinectin (91 mg), factor X (&lt;.5 IU), thrombin (500 IU), synthetic aprotinin (3000 KIU)</td>
<td>2, 4, and 10 mL</td>
<td>$</td>
</tr>
<tr>
<td>VeraSeal / VistaSeal</td>
<td>Grifols</td>
<td>Human fibrinogen and fibrinectin (90 mg), thrombin (500 IU)</td>
<td>2, 4, 6 and 10 mL</td>
<td>$$$</td>
</tr>
</tbody>
</table>

\(^1\) The costs of fibrin glue agents are reported as relative costs as they as the prices for each agent are highly variable and subject to institutional contracting. Price ranges per mL of final mixed fibrin glue (US dollars): $ 60–90 USD, $$ 80–110 USD, $$$ 100–130 USD.
of the defect by direct end-to-end coaptation with fibrin glue (with or without additional sutures); and (3) assessment of at least one of the following outcome measures: functional outcomes, electrophysiology, histopathology, biomechanical outcomes, or operation times. Exclusion criteria were (1) studies reporting on central nerve repair; (2) studies using adhesives other than fibrin glue; (3) studies performing nerve repair using autografts, allografts, or nerve conduits; (4) studies using fibrin glue as a carrier for substances potentially promoting nerve recovery; (5) studies not comparing outcomes of nerve repair with fibrin glue and repair with sutures (this criterion was only applied to animal and cadaveric studies, as comparative studies on humans are limited and we intended to report all available studies on human subjects); (6) non-English studies; and (7) review articles, conference letters, or abstracts. If studies also evaluated other reconstruction techniques (not meeting the inclusion criteria), we only included outcomes of the groups of interest.

Search strategy and study selection

A biomedical information specialist performed a comprehensive systematic search. The Embase, MEDLINE, Cochrane, Web of Science, and Google Scholar databases were searched for English language papers from inception to 25 May 2021. The search included all clinical and experimental studies regarding a combination of “fibrin glue”, “peripheral nerve”, and “nerve repair”. Search syntaxes for the five databases and results per database are depicted in Appendix S1. Two reviewers (C.H. and L.D.) independently screened studies based on title and abstract using Endnote. Subsequently, the full texts of the selected studies were independently evaluated (J.K. and C.H.). Additionally, we screened the reference lists of the included studies and relevant reviews for potentially relevant papers. Differences in selected articles were resolved by consensus.

Data collection

One reviewer (J.K.) extracted data, which were independently checked by a second reviewer (C.H.). Discrepancies were discussed until consensus was reached. Selected articles were divided into three categories: animal, cadaveric, and human studies. We collected the following study characteristics using a standardized extraction form: authors, year, population characteristics, peripheral nerve involved, length of follow-up, sample sizes of the groups of interest, type of fibrin glue, number of sutures, and assessment modalities. Collected data on outcomes were subdivided into five categories: functional outcomes (i.e., motor and sensory function), electrophysiology, histopathology, biomechanical outcomes, and operation times. If data were depicted in graphs only, values were extracted from graphs using a digital software ruler.

Risk of bias

Two reviewers (J.K. and C.H.) independently assessed the methodological quality of all included studies. Disagreements between the reviewers were resolved through discussion and with the assistance of a third reviewer (R.V.). To assess the methodological quality of animal studies, we used the SYRCLE risk of bias tool. This assessment tool consists of ten items addressing six categories of bias (i.e., selection, performance, detection, attrition, reporting, and other bias). Since prior studies demonstrated that experimental details are often inadequately reported in animal studies, we added additional items on the quality of reporting: (1) Is the sample size calculation reported? (2) Is blinding at any level reported? (3) Is randomization at any level reported? (4) Are animal housing conditions reported? (5) Is animal loss reported? (6) Is ethical approval reported? (7) Are any conflicts of interest reported? For methodological quality assessments of cadaveric studies, we used the QUACS criteria. The methodological quality of human studies was assessed using the Cochrane Collaboration risk of bias tool for randomized studies and the MINORS criteria for non-comparative studies.

Data synthesis and statistical analysis

Since the primary objective was to analyze the outcomes of conventional microsurgical repair and fibrin glue (with and without sutures), the experimental groups were divided into three groups: nerve repair with sutures, nerve repair with fibrin glue alone, and nerve repair with a combination of fibrin glue and sutures. Outcome measures were reported following the five outcome categories. If data were reported as means and standard deviation (SD) or standard error of the mean (SEM), results of individual studies were presented as standardized mean differences (SMD) and their 95% confidence intervals (CI). If the SEM was reported, it was converted to SD (SD = SEM × √n). Because of the large variability in outcomes assessments, not all outcomes could be used for meta-analysis. If data were available in at least three studies comparing suture repairs and fibrin glue repairs with or without sutures, results of individual studies were presented in forest plots and pooled by random effect models using the metafor package for R statistical computing. Heterogeneity between combined studies was expressed using the I² statistic. Where statistical pooling was not possible, the findings were presented in narrative form. We did not assess for publication bias because of the low number of studies for each assessment modality.

Results

Search and study characteristics

A PRISMA flow diagram of the complete search results is shown in Figure 1. Following application of inclusion and exclusion criteria, 43 articles were included in this systematic review, and 23 were included in the meta-analyses. Table 2 shows an overview of the characteristics of the included studies. Overall, 37 animal studies, two cadaveric studies, and four human studies were included. Of the included animal studies, most studies were conducted using rat models (78%). The sciatic nerve was most commonly used (76%), followed by the facial nerve (16%), tibial nerve...
(5%), and median nerve (3%). Suture repairs were compared with fibrin glue repairs in 31 studies and with a combination of fibrin glue and sutures in eleven studies. Of the cadaveric studies, one study compared suture repairs with fibrin glue repairs using rabbit sciatic nerves, whereas the other study compared suture repairs with repairs using a combination of fibrin glue and sutures in human tibial and peroneal nerves. The human studies comprised one randomized controlled trial comparing suture repairs with fibrin glue repairs, and three cohort studies evaluating the results of fibrin glue repairs.

Study quality and risk of bias

Results on risk of bias and the reporting of quality indicators of the included animal studies are shown in Figures 2 and 3, respectively. Assessments of the individual studies are depicted in Table S1. Overall, the assessments demonstrate poor reporting of essential methodological details. For example, fifteen studies (41%) reported randomization in some way and nine studies (24%) reported blinding at any level, but none reported any details regarding the procedure. The animal loss was reported in seventeen studies (46%). In three of these studies, animals with dehiscence following fibrin glue repair were either replaced or excluded from electrophysiology and biomechanical testing, resulting in a high risk of attrition bias. In addition, two studies were subject to a high risk of bias on selective outcome reporting. One study only reported functional outcomes for the group with the longest follow-up period and one study reported biomechanical outcomes solely for the fibrin glue group. Selective outcome reporting in the remaining studies was scored as an unclear risk of bias as registration protocols were not available. Assessment of the included cadaveric studies demonstrated moderate to good methodological quality (Table S2). For human studies, the most important concern was the absence of blinding of outcome assessors (Table S3).

Functional outcomes

Twenty-one animal studies examined functional outcomes following nerve repair (Table S4). Assessment modalities reported by at least three studies were the functional index (i.e., walking track analysis),2,25-29 muscle mass,26,28,30-32 and muscle strength,33-35 which were included in the meta-analysis (Figure 4). No differences in functional index were observed between suture repairs and fibrin glue repairs with (SMD -0.03 [95% CI -0.76 to 0.70], I² 45%) or without sutures (SMD 0.33 [95% CI -0.56 to 1.22], I² 72%). Muscle mass was
<table>
<thead>
<tr>
<th>Author(s) &amp; Year</th>
<th>Population</th>
<th>Peripheral nerve</th>
<th>Follow-up</th>
<th>Suture group n</th>
<th>Materials</th>
<th>Fibrin glue group n</th>
<th>Suture + fibrin glue group n</th>
<th>Experimental groups</th>
<th>Assessment modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acar et al., 2020</td>
<td>Wistar-Albino rats, male, adult, 300g</td>
<td>Sciatic nerve</td>
<td>2 months</td>
<td>7</td>
<td>4 sutures</td>
<td>7</td>
<td>1</td>
<td>Tissel®</td>
<td>√</td>
</tr>
<tr>
<td>Akbari et al., 2020</td>
<td>Rats, male, 3-4 months, 250-300 gr</td>
<td>Sciatic nerve</td>
<td>2 months</td>
<td>5</td>
<td>Not reported</td>
<td>5</td>
<td>1</td>
<td>Tissucol®</td>
<td>√</td>
</tr>
<tr>
<td>Attar et al., 2012</td>
<td>Dogs, female, adult, 18-24 kg</td>
<td>Facial nerve</td>
<td>4 months</td>
<td>8</td>
<td>3 sutures</td>
<td>8</td>
<td>1</td>
<td>Tissel®</td>
<td>√</td>
</tr>
<tr>
<td>Becker et al., 1985</td>
<td>Wistar rats, male, 150-200 g</td>
<td>Sciatic nerve</td>
<td>2 months</td>
<td>9</td>
<td>2 sutures</td>
<td>9</td>
<td>Solution of human fibrinogen and 500 NIH thrombin units/ml</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Benfield et al., 2021</td>
<td>Lewis rats, male, 3 months</td>
<td>Sciatic nerve</td>
<td>0 days</td>
<td>10</td>
<td>4 sutures</td>
<td>20</td>
<td>Tissel® (n=10 at each follow-up)</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Bento and Miniti, 1989</td>
<td>Cats, adult, male and female, mean 2146 g</td>
<td>Facial nerve</td>
<td>6 months</td>
<td>10</td>
<td>2 sutures</td>
<td>10</td>
<td>Solution of human fibrinogen, fibronectin, factor XIII, plasminogen, aprotinin and 500 IU/ml bovine thrombin</td>
<td>√</td>
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<td>Boedts, 1987</td>
<td>Laboratory rats</td>
<td>Sciatic nerve</td>
<td>0-3 months</td>
<td>10</td>
<td>Not reported</td>
<td>10</td>
<td>Solution of fibrinogen and thrombin</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Breshah et al., 2013</td>
<td>Albino rats, 280-300 g</td>
<td>Sciatic nerve</td>
<td>1 month</td>
<td>5</td>
<td>Not reported</td>
<td>5</td>
<td>Solution of fibrinogen and thrombin</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Buchaim et al., 2016</td>
<td>Wistar rats, male, aged 60 days, mean 250 g</td>
<td>Facial nerve</td>
<td>1 month</td>
<td>8</td>
<td>Not reported</td>
<td>8</td>
<td>Fibrin glue derived from snake venom (CEVAP)</td>
<td>√</td>
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<tr>
<td>Cruz et al., 1986</td>
<td>Sprague-Dawley rats, male, 275-300 g</td>
<td>Sciatic nerve</td>
<td>2 months</td>
<td>10</td>
<td>6 sutures</td>
<td>10</td>
<td>Solution of autologous fibrinogen and thrombin</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Erfanian et al., 2014</td>
<td>Wistar rats, male, mean 266 ± 44 g</td>
<td>Sciatic nerve</td>
<td>2 months</td>
<td>8</td>
<td>3 sutures</td>
<td>8</td>
<td>Solution of fibrinogen and thrombin</td>
<td>1 sutur + solution of fibrinogen and thrombin</td>
<td>√</td>
</tr>
<tr>
<td>Farrag et al., 2006</td>
<td>Sprague-Dawley rats, male, 250-300 g</td>
<td>Facial nerve</td>
<td>2 months</td>
<td>11</td>
<td>2 sutures</td>
<td>12</td>
<td>Tissel®</td>
<td>2 sutures + Tissel</td>
<td>√</td>
</tr>
<tr>
<td>Feldman et al., 1987</td>
<td>New Zealand rabbits, male, 2.0-3.0 kg</td>
<td>Sciatic nerve</td>
<td>2 months</td>
<td>6</td>
<td>2 sutures</td>
<td>6</td>
<td>Solution of autologous fibrinogen, factor XIII and 500IU/ml thrombin</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Felix et al., 2013</td>
<td>C57/B16 mice, adult</td>
<td>Sciatic nerve</td>
<td>2 months</td>
<td>5</td>
<td>2 sutures</td>
<td>5</td>
<td>Beriplast</td>
<td>√</td>
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<table>
<thead>
<tr>
<th>Author(s) &amp; Year</th>
<th>Population</th>
<th>Peripheral nerve</th>
<th>Follow-up</th>
<th>Suture group</th>
<th>Fibrin glue group</th>
<th>Suture + fibrin glue group</th>
<th>Assessment modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goncharuk et al., 2020</td>
<td>Purebred rats, male, 5-6 months, 250 ± 25 g</td>
<td>Sciatic nerve</td>
<td>1 month</td>
<td>5</td>
<td>4-6 sutures</td>
<td>5</td>
<td>2 sutures + Tisseel</td>
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<td>Inaloz et al., 1997</td>
<td>Wistar-Albino rats, 200-250 g</td>
<td>Sciatic nerve</td>
<td>1 month</td>
<td>15</td>
<td>Not reported</td>
<td>15</td>
<td>Tisseel®</td>
</tr>
<tr>
<td>Junior et al., 2004</td>
<td>New-Zealand rabbits, male, 2.5-3.0 kg</td>
<td>Facial nerve</td>
<td>2 weeks</td>
<td>3</td>
<td>Not reported</td>
<td>3</td>
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<td>Knox et al., 2013</td>
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<td>Facial nerve</td>
<td>3.5 months</td>
<td>8</td>
<td>2 sutures</td>
<td>8</td>
<td>Solution of fibrinogen and thrombin</td>
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<tr>
<td>Lee et al., 2020</td>
<td>C57BL/6J mice, adult, 20-25 g</td>
<td>Sciatic nerve</td>
<td>1 month</td>
<td>10</td>
<td>4 sutures</td>
<td>10</td>
<td>Tisseel®</td>
</tr>
<tr>
<td>Leite et al., 2019</td>
<td>Wistar rats, male, adult, 300 - 400 g</td>
<td>Sciatic nerve</td>
<td>2 months</td>
<td>9</td>
<td>3 sutures</td>
<td>9</td>
<td>1 suture + fibrin glue derived from snake venom (CEVAP)</td>
</tr>
<tr>
<td>Lin et al., 2010</td>
<td>Sprague-Dawley rats, 250-300 g</td>
<td>Sciatic nerve</td>
<td>1 week</td>
<td>24</td>
<td>4 sutures</td>
<td>24</td>
<td>Beriplast P</td>
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<tr>
<td>Maragh et al., 1990</td>
<td>Sprague-Dawley rats, male, 402-543 g</td>
<td>Sciatic nerve</td>
<td>2 months</td>
<td>6</td>
<td>6</td>
<td></td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td>Martins et al., 2005</td>
<td>Wistar rats, male, 260-355 g</td>
<td>Sciatic nerve</td>
<td>6 months</td>
<td>28</td>
<td>28 sutures</td>
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<td>Beriplast P</td>
</tr>
<tr>
<td>Menovsky and Beek, 1987</td>
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<td>Sciatic nerve</td>
<td>4 months</td>
<td>8</td>
<td>4-6 sutures</td>
<td>8</td>
<td>2 sutures + Tissucol®</td>
</tr>
<tr>
<td>Nishimura et al., 2008</td>
<td>Isogenic New Zealand rabbits, adult</td>
<td>Tibial nerve</td>
<td>1 week</td>
<td>2</td>
<td>3-6 sutures</td>
<td>2</td>
<td>4 sutures + Tissucol®</td>
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<tr>
<td>Nishimura et al., 2008</td>
<td>Isogenic New Zealand rabbits, adult</td>
<td>Sciatic nerve</td>
<td>1 hour</td>
<td>12</td>
<td>12 sutures</td>
<td>12</td>
<td></td>
</tr>
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<td>Isogenic New Zealand rabbits, adult</td>
<td>Sciatic nerve</td>
<td>1 week</td>
<td>12</td>
<td>12 sutures</td>
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<td>12 sutures</td>
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<td>15 sutures</td>
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<td>Author(s) &amp; Year</td>
<td>Population</td>
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<td>Follow-up</td>
<td>Suture group</td>
<td>Fibrin glue group</td>
<td>Suture + fibrin glue group</td>
<td>Assessment</td>
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<td></td>
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<td>4</td>
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<td>5-76 years</td>
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Abbreviations: B, biomechanical outcomes; E, electrophysiology; F, functional outcomes; H, histology; O, operation times.
higher in suture repairs than in fibrin glue repairs (SMD -0.51 [95% CI -0.86 to -0.17], $I^2$ 0%), whereas no difference was observed when fibrin glue was combined with sutures (SMD 0.01 [95% CI -0.53 to 0.55], $I^2$ 0%). Muscle strength was only compared between suture repairs and fibrin glue repairs without sutures and did not differ (SMD 0.19 [95% CI -0.33 to 0.71], $I^2$ 0%).

The studies that were not included in the meta-analysis considered other measures of motor functional recovery, including footprint measures,\textsuperscript{16,36,37} toe contracture,\textsuperscript{31,38} whisking amplitude,\textsuperscript{5,39} and facial asymmetry.\textsuperscript{40} In addition, three studies reported functional index results as medians or means only and were not included in the meta-analysis.\textsuperscript{31,41,42} Of these, five studies found no statistical differences between the suture group and fibrin glue group.\textsuperscript{5,16,36,38,40} However, five studies found better results in the suture group, regarding a higher functional index,\textsuperscript{31,41,42} a lower percentage of severe toe contractures,\textsuperscript{31} and better whisker movements.\textsuperscript{39} In contrast, another study found that footprint lengths were closer to normal in the fibrin glue repairs.\textsuperscript{37}

**Electrophysiology**

Fourteen animal studies assessed electrophysiology outcomes, of which eleven were included in the meta-analysis\textsuperscript{1,8,27,28,41-47} (Figure 5). We found no differences in amplitude between suture repairs and fibrin glue repairs with (SMD 0.18 [95% CI -0.25 to 0.61], $I^2$ 0%) or without sutures (SMD -0.10 [95% CI -0.89 to 0.69], $I^2$ 56%). Conduction velocity did not differ between suture repairs and fibrin glue repairs with (SMD 0.52 [95% CI -0.21 to 1.25], $I^2$ 0%) or without sutures (SMD -0.12 [95% CI -0.46
Figure 4 Forest plots of functional outcomes. The left figure depicts all studies comparing nerve repair with fibrin glue and nerve repair with sutures, whereas the right figure demonstrates studies comparing nerve repair with a combination of fibrin glue and sutures and nerve repair with sutures. Abbreviations: df, degrees of freedom; CI, confidence interval; SMD, standardized mean difference.

Figure 5 Forest plots of electrophysiology outcomes. The left figure depicts all studies comparing nerve repair with fibrin glue and nerve repair with sutures, whereas the right figure demonstrates studies comparing nerve repair with a combination of fibrin glue and sutures and nerve repair with sutures. Abbreviations: df, degrees of freedom; CI, confidence interval; SMD, standardized mean difference.

to 0.21], I² 0%). No differences in latency were observed between suture repairs and fibrin glue repairs with (SMD -0.09 [95% CI -0.72 to 0.54], I² 45%) or without sutures (SMD 0.30 [95% CI -0.36 to 0.95], I² 13%). Three studies reported results as medians39 or means only37,38 and were not included in the meta-analysis. Two studies found no differences between suture repairs and fibrin glue repairs with 39 or without sutures.39,48 Yet, one study found a higher conduction velocity and amplitude in fibrin glue repairs.37

Histology
Thirty-four studies assessed histological outcomes,1,2,7,8,15,16,25,36,38–53 although there was considerable
variability in the outcome measures that were evaluated (Table 55). The four most frequently evaluated outcomes were dehiscence, fiber count, fibrosis, and inflammation (Figure 6). Dehiscence was assessed in 20 studies. None reported dehiscence in repairs with sutures or a combination of fibrin glue and sutures. In contrast, six of sixteen studies reported dehiscence in repairs using fibrin glue alone, ranging from 6 to 80%. Furthermore, the majority of studies found no differences in fiber count between groups. Considering inflammation and fibrosis, results were inconsistent between studies.

Biomechanical outcomes

Four animal studies\(^1\,33,44\,54\) and two cadaveric studies\(^55,56\) evaluated biomechanical outcomes, of which five were included in the meta-analysis (Figure 7). Suture repairs yielded a higher strength than repairs with fibrin glue alone (SMD -0.86 [95% CI -1.28 to -0.44], \(I^2 = 29\%\)). However, strength did not differ between suture repairs and repairs with a combination of fibrin glue and sutures (SMD -0.47 [95% CI -2.07 to 1.13], \(I^2 = 84\%\)). One study reported results as means only and could not be included in the meta-analysis.\(^54\) They found that suture repairs yielded a higher resistance to rupture at 0 and 7 days, whereas no differences between suture and fibrin glue repairs were found at 14 and 28 days after repair.

Figure 6 Overview of the four most frequently reported histology outcomes. The left figure depicts all studies comparing nerve repair with fibrin glue and nerve repair with sutures, whereas the right figure demonstrates studies comparing nerve repair with a combination of fibrin glue and sutures and nerve repair with sutures. Results are presented as the percentage of studies reporting either favorable results for one of the repair techniques or no difference between groups.

Figure 7 Forest plots of biomechanical outcomes. The left figure depicts all studies comparing nerve repair with fibrin glue and nerve repair with sutures, whereas the right figure demonstrates studies comparing nerve repair with a combination of fibrin glue and sutures and nerve repair with sutures. Abbreviations: df, degrees of freedom; CI, confidence interval; SMD, standardized mean difference.

Operation times

Five studies evaluated operation times (Figure 8). In general, the use of fibrin glue resulted in 3-4 times shorter operation times compared to suture repairs.\(^5,14,36,44\) Only one study examined operation times of repair with fibrin glue and sutures combined.\(^48\) They demonstrated that this technique was 1.6 times faster than repair with sutures alone.

Human studies

The search identified four human studies that evaluated outcomes of fibrin glue repairs,\(^57-60\) of which one study compared outcomes of suture repairs and fibrin glue repairs. This recently published randomized controlled trial evaluated motor and sensory recovery following median or ulnar nerve repair with autologous fibrin glue or sutures.\(^57\) They found that both repair groups had regained similar motor and sensory function at the final follow-up. More specifically, 80% of the suture repairs and 78% of the fibrin glue repairs regained a useful motor recovery (i.e., grade M3 or higher). For sensory recovery, 76% of the suture repairs and 63% of the fibrin glue repairs achieved a sensory function of grade S3 or higher. In addition, no significant differences were found in grip strength, Michigan Hand Outcomes Questionnaire scores, electrophysiology outcomes, or postoperative complications. A prospective cohort study examined...
end-to-end repair of the facial nerve using fibrin glue alone in thirteen patients. Sixteen months postoperatively, 85% of patients were satisfied and demonstrated mild to moderate dysfunction. A retrospective cohort study also evaluated functional outcomes following facial nerve repair with fibrin glue, using the House-Brackmann grading system and eFACE scale at a minimum follow-up of one year. End-to-end coaptation was performed in three of 36 nerve repairs. All three patients reached a House-Brackmann grade 3 and a mean eFACE score of 76, indicating satisfactory outcomes. In addition, Egloff and Narakas performed nerve repairs using fibrin glue on a variety of peripheral nerves, ranging from the brachial plexus to digital nerves. Overall, they concluded that results were comparable to conventional suture repair.

Discussion

The use of fibrin glue for peripheral nerve surgery is currently used in clinical settings worldwide because of its ease of use, less tissue manipulation, fewer sutures, and shorter operation times. However, its application is still considered off-label as the most essential question remains whether fibrin glue also results in similar nerve recovery. Therefore, this study aimed to provide a comprehensive overview of the use of fibrin glue for peripheral nerve repair and compare the outcomes with conventional suture repair. Our findings indicate that nerve regeneration may be similar in fibrin glue repairs and suture repairs, and a combination of both. However, the use of fibrin glue alone resulted in more dehiscence. Combining fibrin glue with one or two positional sutures allows for a precise realignment of the nerve fibers and yields sufficient strength to prevent dehiscence.

Current literature on fibrin glue for peripheral nerve injury primarily consists of basic research using animal models. Particularly, rat models are frequently used due to the high rate of nerve regeneration and the availability of genetically similar strains, allowing for well-controlled comparisons between techniques. However, there is a large between-study variation in the assessment modalities, which often impedes comparisons between studies. One of the most frequently used assessment modalities for motor nerve recovery is the compound motor action potential. An advantage of this technique is that the amplitude and latency parameters are easy to interpret due to their uniformity of observations. However, this technique also yields limitations as the outcomes are influenced by several factors, including the location of the electrodes and the temperature. The isometric tetanic force is currently considered the most reliable assessment modality for motor nerve regeneration, although it is a technically demanding and time-consuming procedure that can only be performed after animal sacrifice. The sciatic functional index is frequently used as it allows for serial measurements. However, the outcomes are influenced by the speed of walking, autotomy, and toe contractions. Furthermore, it has been shown that this walking track analysis poorly correlates with isometric tetanic force and electrophysiology outcomes. These findings indicate that not all assessment modalities are equally reliable measures of nerve regeneration. Hence, as each assessment modality yields limitations, the outcomes should not be interpreted independently but in the light of the other modalities.

We found no differences in the functional index, muscle strength, and electrophysiology outcomes between suture repairs and fibrin glue repairs with or without sutures in this study. Muscle mass did not differ between suture repairs and fibrin glue repairs with sutures, whereas fibrin glue alone resulted in a lower muscle mass. These satisfactory results of fibrin glue on various assessment modalities for nerve recovery indicate that fibrin glue repairs allow for sufficient nerve recovery in experimental studies. This is also in line with the findings reported in human studies. A recently published randomized controlled trial demonstrated no differences in

<table>
<thead>
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<th>Author</th>
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<tr>
<td><strong>Fibrin glue vs. Suture</strong></td>
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<td><strong>Fibrin glue + suture vs. Suture</strong></td>
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<td>Moy</td>
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Figure 8 Relative operation times of nerve repair using fibrin glue (with or without sutures) compared to repair using sutures. As only three of five studies reported operation times as mean and standard deviation, results are presented as a percentage of the operation time in the suture group.
motor and sensory function between fibrin glue repairs and suture repairs. These findings from both experimental and clinical studies suggest that suture repairs and fibrin glue repairs result in comparable nerve regeneration.

Although fibrin glue repairs demonstrated satisfactory outcomes regarding nerve regeneration, the use of fibrin glue alone resulted in lower strength and more dehiscence compared to suture repairs. Biomechanical strength was assessed by measuring the force needed to separate the coaptation. It is therefore not surprising that suture repairs yield a higher strength. The nerve repair should ideally be a tension-free coaptation with enough strength to prevent dehiscence.\textsuperscript{71, 72} Six of sixteen studies reported dehiscence of fibrin glue repairs in the present study, ranging from 6\% to 80\%. In contrast, no cases of dehiscence were reported when fibrin glue was combined with one or two sutures, indicating that fibrin glue should ideally be combined with one or two strengthening sutures to prevent dehiscence.

Beside sufficient strength to prevent dehiscence, adding one or two sutures to fibrin glue repairs yields further advantages that may improve outcomes. First, it is generally recognized that outcomes following nerve repair largely depend on the adequate alignment of nerve fascicles. This particularly applies to mixed motor and sensory nerve repairs, since improper realignment of motor and sensory fascicles could result in good regeneration but poor functional outcomes.\textsuperscript{73} The addition of one or two positional sutures enables the surgeon to achieve a precise realignment of the fascicles. Second, the additional sutures provide more strength to allow for early postoperative mobilization, preventing adhesions and improving functional outcomes.\textsuperscript{71, 72, 74}

Furthermore, our results demonstrate that the use of fibrin glue significantly reduced operation times, which may pose both clinical and economic benefits. Despite the higher equipment costs of fibrin glue compared to sutures, several cost-effectiveness studies on conjunctival fixation and hernia repair found that the reduction in operation times significantly reduced the total surgery expenses.\textsuperscript{70, 77} Future studies may examine the cost-effectiveness of fibrin glue in peripheral nerve repair.

An important issue to address is whether the use of fibrin glue is associated with more complications. Allergic reactions, including anaphylaxis, have been reported in few case reports with an estimated incidence of 0.5 per 100,000 applications.\textsuperscript{78-80} Furthermore, some suggest that excess application of topical agents may increase the risk of surgical site infections and impair wound healing. In this systematic review, only one of the included human studies reported on complications.\textsuperscript{77} Although they observed few cases of superficial wound infections, the incidence did not differ between the fibrin glue and suture repair groups. Interestingly, meta-analyses on other surgical interventions (e.g., vascular surgery, hernia repair, and urethroplasty) concluded that the use of fibrin glue did not affect or even reduced wound-related complications.\textsuperscript{81-84} These findings indicate that topical application of fibrin glue is relatively safe. However, although extremely rare, anaphylaxis is a serious adverse event that should be considered when changes in vital signs are observed following the application of fibrin glue.

Although fibrin glue has gained a pivotal role in the approach for peripheral nerve repair in our clinical practice, some important technical considerations should be made. Based on our personal experience and recommendations provided by Siquera and Martins,\textsuperscript{85} the following practical remarks should be taken into account: First, direct end-to-end repair should only be performed when the nerve gap is small enough to avoid excessive tension. This is especially important since nerve repair with fibrin glue has a low initial strength. In our clinical practice, we therefore use a minimum of two epineural sutures, depending on the diameter of the nerve, to align the nerve stumps and strengthen the coaptation, followed by the application of fibrin glue. To achieve a proper alignment, the nerve stumps should be trimmed to reveal the healthy epineurium and fascicular structure. Identification of the longitudinal epineural vasculature facilitates accurate alignment. Furthermore, the sutures should be passed only through the epineurium to prevent scar tissue formation resulting from the incorporation of nerve fascicles. Second, it is imperative to perform a meticulous hemostasis since bleeding may cause distortion of the nerve architecture and excessive fibrosis. To ensure optimal adherence of the fibrin glue, the surface of the nerve stumps should also be free of excess fluids prior to its application and should be allowed to dry for at least five minutes before irrigation. Third, we recommend that the postoperative immobilization period of the affected limb should be similar to peripheral nerve repairs with sutures to guarantee an optimal environment for nerve regeneration, while minimizing adhesions and stiffness.\textsuperscript{71, 72, 74}
ligence of assessment methods to reduce bias, impeding the possibility to draw reliable conclusions from these animal studies. However, as insufficient reporting does not necessarily imply that the methodology of a study is inadequate, all studies meeting the inclusion criteria were included. To further improve the reliability, comparability, and translatability of animal studies in research, adherence to guidelines for the reporting of animal studies (e.g., the ARRIVE guidelines) is essential.

Conclusions

This study provides a comprehensive overview of available literature on fibrin glue for peripheral nerve repair. Our findings indicate that nerve regeneration may be similar in fibrin glue repairs and suture repairs. Yet, it is highly recommended to combine fibrin glue with one or two positional sutures to allow for a precise realignment of the nerve fibers and provide sufficient strength to prevent dehiscence. It should be noted, however, that most studies were performed in animal models. We recommend that well-controlled human studies should be conducted to further confirm the efficacy of fibrin glue for peripheral nerve repair in clinical setting.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgments

The authors would like to thank Wichor Bramer, biomedical information specialist at the Erasmus MC University Medical Center, for assisting with the systematic search strategy and syntax.

Funding sources

This work was funded by ZonWw (Project Number: 114024161) in the program ‘Meer Kennis met Minder Dieren’ (MKMD). ZonWw had no role in the study design and collection, data analysis, interpretation of data, or writing the manuscript.

Ethical approval

Not required.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j bjps.2022.01.007.

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