INTRAOCULAR APPLICATION OF FIBRIN GLUE AS AN ADJUNCT TO PARS PLANA VITRECTOMY FOR RHEGMATOGENOUS RETINAL DETACHMENT

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Purpose: To evaluate the efficacy of intraocular application of fibrin glue to seal the retinal breaks during standard pars plana vitrectomy for primary rhegmatogenous retinal detachment.

Methods: Twenty-six eyes of 26 rhegmatogenous retinal detachment patients were included in the study. Fibrin glue was used to seal the retinal breaks during standard pars plana vitrectomy in all 26 eyes. Each eye was completely filled with a balanced saline solution at the end of the surgery. The success rate of the reattachment surgery, change in best-corrected visual acuity, intraocular pressure, and occurrence of intraoperative and postoperative complications were recorded and analyzed.

Results: All eyes, with a mean age of 45.1 ± 18.3 years, were treated with pars plana vitrectomy surgery. During pars plana vitrectomy surgery, the fibrin glue showed excellent adherence and compliance to the retina. The glue was no longer visible through ultrasound scan 14.85 ± 4.56 days after surgery. The retinal breaks were sealed completely, and retina attached in all 26 eyes with no occurrence of rhegmatogenous retinal detachment during the follow-up period. The best-corrected visual acuity at 6 months after operation was significantly improved from preoperation best-corrected visual acuity. After operation, two eyes (2/26) developed an epiretinal membrane. Although three eyes (3/26) had a transient increased intraocular pressure during the 1st week after surgery, the intraocular pressure lowered to the normal range after the application of timolol. One eye (1/26) required daily topical antiglaucoma drops to lower the intraocular pressure. No adverse effects of fibrin glue were observed.

Conclusion: The fibrin glue provided a superior adhesive effect for sealing retinal breaks, while showing no additional adverse effects. It is a worthy alternative to gas tamponade for rhegmatogenous retinal detachment vitrectomy surgery.

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Rhegmatogenous retinal detachment (RRD) is a severe, potentially vision-threatening disease. As the name implies, RRD is preceded by a discontinuity or breaks in the retina, through which subretinal fluid can accumulate in the potential space between the neurosensory retina and the underlying retinal pigment epithelium.1,2 The most important step for RRD treatment is to anatomically seal the retinal breaks and reattach the retina. Pars plana vitrectomy (PPV) is now often used to repair RRD, but PPV is dependent on endotamponade agents such as air, gas, or silicone oil to avoid the passage of fluid through the retinal break into the subretinal space.3 According to the literature, surgical success rates for RRD repair vary from 76.9% to 96.1%. These techniques are not always successful, particularly in RRD patients with inferior breaks.4–7 Endotamponade agents may cause some severe complications, which include cataract formation, secondary glaucoma, positioning restrictions, and corneal degeneration.8,9 The reduction of these

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complications has become a major issue; therefore, a new alternative method to facilitate PPV needs to be investigated.

During the past two decades, fibrin glue has gained popularity as an adjunct in many surgical fields and endoscopic procedures. It has shown significant utility in the fields of microsurgery, burns, gynecological and ophthalmic surgery as a hemostatic agent, adhesive, and tissue-approximating agent used to prevent postoperative bleeding, delayed perforation, and stenosis. Multiple studies have reported its safety and efficacy.\textsuperscript{10–12} Fibrin glue (fibrin adhesive; fibrin sealant) is a hemostatic and wound-support product consisting of the blood coagulation factors fibrinogen, factor XIII and thrombin, the antifibrinolytic agent aprotinin, and calcium chloride. Fibrin sealants can be used in sealing pleural defects and have also been used to successfully seal cerebrospinal fluid leaks after trauma or surgery. In addition, it is also safe and effective as a treatment for perianal fistulas.\textsuperscript{13–16} Fibrin glue has also been widely used in ophthalmic surgery because it is an alternative to sutures for securing conjunctival grafts, for intraocular lens fixation, and corneal wound closure, and healing.\textsuperscript{17–20} The clinical application of fibrin glue is generally considered safe.\textsuperscript{21} The aim of this article is to report the use of commercially available fibrin glue in sealing retinal breaks during PPV. To the best of authors’ knowledge, this is the first reported use of fibrin glue in the clinical management of RRD.

Materials and Methods

Materials

Beixiu Porcine Fibrin Sealant Kit. It is composed of major fibrin sealant, thrombin, major sealant solution (phosphate buffer), and catalyst solution ($\text{CaCl}_2$ solution).

Patients and Methods

A retrospective chart series of 26 surgeries were performed on 26 patients (26 eyes) with primary RRD in our hospital between January 2014 and July 2017. The following preoperative patient characteristics were retrospectively reviewed (Table 1): age, sex, Snellen visual acuity using pinhole acuity testing, intraocular pressure (IOP), symptom duration, size and location of retinal breaks, and extent of detachment (including macular involvement). Inferior detachments were defined as those confined to the inferior 6 clock hours of the fundus. Patients with a history of ocular surgery were excluded. Because the Fibrin Sealant Kit is not labeled for the use under discussion, written consent was obtained from all participants. The ethical committee of the third medical center of Chinese PLA’s General Hospital approved this study in accordance with the Helsinki declaration.

Surgery

All the patients underwent a standard, 3-port, 23-gauge PPV with the application of fibrin glue by the same surgeon. After complete postvitreous detachment, perfluorocarbon liquids were used to reattach the retina. A flute needle was used to draw the subretinal fluid from the original breaks with no retinotomies or other retinal holes made for drainage. After fluid–air exchange, all the retinal breaks and the retinal lattice degeneration sites were treated using an endolaser under air condition. The fibrin glue was reconstituted according to the manufacturer’s instructions 5 minutes before use. Before applying the fibrin glue, it is essential to remove as much subretinal fluid as possible; in a peripheral retinal break, this can be very challenging to surgeons. The retinal break was gently covered with 50-$\mu\text{L}$ fibrin glue A mixed with trypan blue by using a 23-gauge needle; this can provide sufficient coverage of the whole retinal break, especially the edge of the break. Five seconds later, mixture B was applied to the surface of the break, which was already covered by the glue A. Local adhesion of the edges of the retinal break to the underlying choroid

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total</th>
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<tr>
<td>Sex</td>
<td></td>
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<tr>
<td>Male</td>
<td>12</td>
</tr>
<tr>
<td>Female</td>
<td>14</td>
</tr>
<tr>
<td>Age, mean ± SD, years</td>
<td>45.1 ± 18.3</td>
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<tr>
<td>Duration of symptoms, days</td>
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<tr>
<td>No. of retinal breaks</td>
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<td>Single</td>
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<tr>
<td>Multiple</td>
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<tr>
<td>Location of breaks</td>
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<td>Superior and/or midline</td>
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<tr>
<td>Inferior</td>
<td>8</td>
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<tr>
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<td>10</td>
</tr>
<tr>
<td>B</td>
<td>14</td>
</tr>
<tr>
<td>C1</td>
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</tr>
<tr>
<td>With high myopia</td>
<td>13</td>
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<td>21</td>
</tr>
<tr>
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Table 1. Demographic and Preoperative Clinical Characteristics of Patients
was noted, and the retinal break edges were well sealed. The application of fibrin glue must be precise and quick so that the glue can form a perfect membrane covering the retinal break. Three minutes later, air–fluid exchange was performed, and any excess fibrin membrane was removed. The peripheral retina was checked before finishing the surgery to ensure that there was no other retinal hole or lattice degeneration. All eyes were completely filled with balanced saline solution at the end of the surgeries (surgery videos can be found in Videos, Supplemental Digital Contents 1 and 2, http://links.lww.com/IAE/B18 and http://links.lww.com/IAE/B19, respectively). Finally, subconjunctival administration of dexamethasone was given to all 26 eyes.

Statistical Analysis

Primary success was defined as the retina remaining reattached for at least 6 months after the primary surgery. Macular complication was defined as epiretinal membrane (ERM) that required surgical intervention. The primary outcome measure was the proportion of patients with visual success (defined as visual acuity improvement ≥15 letters at the 6-month follow-up compared with the baseline visual acuity). Statistical analysis and main outcome measure: the visual acuity was converted to the logarithm of the minimum angle of resolution for statistical analysis. Hand motion visual acuity was converted to 2.28 logarithm of the minimum angle of resolution according to previous investigation.

Results

The details of the sex and age of the patients involved in this study, as well as their preoperative clinical characteristics, are given in Table 1. The mean follow-up period was 13.14 ± 6.00 months. One patient was lost to follow-up 9 months after operation.

Anatomical Success

During vitrectomy surgery, the fibrin glue showed excellent adherence and compliance to the retina. When applied to the retina, this gives a temporary solidified translucent glue membrane that can be recognized from the ultrasound scan image (Figure 1). This membrane was completely absorbed and was no longer visible with direct ophthalmoscopy in 14.85 ± 4.56 days (Figure 2). The retinal breaks were sealed completely with fibrin glue, and the primary anatomical reattachment rate was achieved in all 26 eyes (100%) with no occurrence of RRD during the follow-up period. The main outcome measure for the study was single surgery anatomical success, which was defined as one operation to anatomically reattach 100% of the retina for 3 months or during the whole follow-up period.

Best-Corrected Visual Acuity

At baseline, 11 patients (42.31%) had a best-corrected Snellen visual acuity of ≤2/20, whereas 6 months after operation, 16 patients (61.54%) had a best-corrected Snellen visual acuity of ≥20/66. Best-corrected Snellen visual acuity at baseline ranged from 20/3,000 to 20/20, and the 6-month postoperative best-corrected Snellen visual acuity ranged from 20/2,000 to 20/20. The difference between the 6-month postoperation and preoperation best-corrected visual acuity (logarithm of the minimum angle of resolution) was of statistical significance (P = 0.006238). At 6 months after operation, an increase of visual acuity was seen in 14 cases (53.85%) that gained more than 15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters. In seven cases (26.92%), the visual acuity remained the same. In four cases (15.34%), the visual acuity remained stable (loss ≤15 ETDRS letters), and one case (3.85%) lost 15 ETDRS letters.

Intraocular Pressure

The preoperation IOP was 13.50 ± 3.21 mmHg (range, mmHg). Of the 26 eyes, 22 had a normal IOP over the entire follow-up. Three eyes had a transient increased IOP during the first week after surgery, which lowered to the normal range after the application of timolol. One eye required daily topical antiglaucoma drops to lower the IOP.

Epiretinal Membrane Formation

Two cases (7.69%) developed an ERM at 3 and 4 months after surgery, which required an additional membrane peeling surgery.

Safety Evaluation

There were no severe ocular inflammations or systemic adverse events observed during the follow-up. No other ophthalmoscopically visible changes were noted in these eyes. No traction or retinal detachment was noted during the follow-up.

Discussion

To successfully reattach the retina, the first key factor is to create solid chorioretinal adhesion around the retinal breaks with an endolaser. Weak chorioretinal adhesion is caused by the proteinaceous
coagulum around the retinal breaks in the first three days after endolaser treatment; this develops into a strong inflammatory-based scar beginning at about Day 5 after photocoagulation. The other key factor to observe is the prevention of fluid going into the subretina through the retinal breaks before a solid chorioretinal adhesion has formed. During RRD surgeries, endotamponade agents are used to provide surface tension across the retinal breaks, which prevents fluid flowing into the subretinal space until the chorioretinal adhesion is solid and permanent. PPV plus expansile gas tamponade is a major surgical technique for RRD in modern times. The role of gas bubbles is to keep the retina dry and provide a force to facilitate stable chorioretinal adhesion, with the former considered to be more important. However, previous studies have found that long-acting expansile gas or silicone oil tamponade can cause many complications, such as IOP elevation, vitreous disturbance, cataract formation, proliferative vitreoretinopathy, and new breaks in the retina. The gas bubble is also believed to provide a scaffold that in turn provides a support
allowing for a bridging preretinal membrane to form. Another factor that restricts the application of gas tamponade is the location of the retinal breaks, which also has an important role to play in the success of the retinal reattachment surgery. The inferior breaks usually need silicone oil tamponade, which would require additional surgery to remove the silicone oil from the eye.\(^{30,31}\)

Face-down and other positions are another limitation of PPV with gas tamponade surgery. These positions are an integral component for retinal detachment surgery using PPV with gas tamponade, in theory, by allowing for maximal coverage of the retinal breaks with a gas tamponade agent through a buoyancy or surface tension effect. Although the mechanism, duration, and advantage of the face-down position remain controversial, its practice remains prevalent in PPV surgery. The postoperative requirement after PPV with gas tamponade to maintain the face-down position for weeks is uncomfortable for all patients, whereas compliance is impossible for some people, such as victims of severe trauma, elderly patients, or those who suffer from neck and back problems.\(^{32}\) Also, an incorrect face-down position can affect surgical outcomes.\(^{33–35}\)

Fibrin glues are effective in attaching opposing wound edges quickly and are also used to achieve hemostasis, to seal or glue tissues, and to help healing without inducing severe inflammation or foreign-body reactions. As such, we believed that it could be used as an alternative to gas tamponade for PPV surgery. The rationale for the application of fibrin glue in the surgery of RRD is based on the theory that once the fibrin glue membrane has formed, it can prevent fluid flow into the subretinal space until the chorioretinal adhesion has formed firmly. In the study, all 26 eyes reached primary anatomical success after PPV surgery during the follow-up period. Success rates of 76.9% to 96.1% are reported for primary surgeries for RRD, and to an extent, preoperative findings can be used to assess the chance of success in individual cases.\(^{4–7}\)

We assumed that fibrin glue may facilitate the fibrosis around the retinal break and promote the bonding of the retina and retinal pigment epithelium layer, even as the fibrin glue degrades.

The excellent adherence to the retina showed by fibrin glue could potentially stop the leakage of retinal pigment epithelium cells and inflammatory factors into the vitreous cavity, which may lower the risk of ERM formation after surgery. Epiretinal membrane formation is a common complication of RRD surgery. The incidence of ERM after RRD surgical repair has been reported to range from 4.4% to 12.8%.\(^{36–38}\) In the study, two eyes (7.69%) developed ERM after vitrectomy, demonstrating that the application of fibrin glue does not increase the risk of ERM formation. Owing to the limitation of the sample size, it cannot be conclusively stated whether the ERM formation in these two eyes is related to the use of fibrin glue; therefore, further study is needed.

The evaluation of safety and potential inflammatory responses in vivo is of critical importance in the application of any biomaterial. In this regard, we have already determined that there was not any significant inflammatory response or retinal toxicity in rabbits, the results of which were published in a Chinese journal named Yanke in 2015. In China, Beixiu sealant is now widely used, both commercially and in the departments of general surgery, cardiothoracic surgery, obstetrics and gynecology orthopedics, neurosurgery, and urology for managing bleeding, sealing or gluing wounds, promoting wound healing, preventing tissue adhesion, or drug reliever. In the study, no obvious inflammatory signs were found in the anterior or posterior segments. Biologic tissue glues have been of interest in ophthalmic applications, and fibrin glues have been tested experimentally in the eye as far back as the 1970s.\(^{39}\) Reports on the adhesive powers of these tissue glues in conjunctival, corneal cataract, and retinal surgeries were encouraging from the late 1940s.\(^{40}\) Nevertheless, the lack of clinical data on the use of fibrin sealants in the intraocular environment is starkly evident. Related earlier studies described fibrin sealant only as an adjunct to suturing, whereas this trial evaluated it as the sole agent for intraocular use for PPV surgeries.

There are further risks to consider with the use of fibrin glue; the transmission of infectious agents and immune or allergic reactions. Beixiu glue, which is derived from pigs, is biological and biodegradable and presents good adhesive function with few adverse effects. This commercially available fibrin glue is virus-inactivated and has been checked for viral antigen and antibodies, so the chance of infection transmission is very low.

We consider that the ideal ocular adhesive glue should have adequate tensile strength to seal the retinal breaks, not cause inflammation or toxicity, and eventually be absorbed after the retina has been fully reattached at the adhesive interface. Our results are promising. The application of fibrin glue successfully sealed all the retinal breaks, significantly reduced the complications of gas and silicone oil tamponade, improved the comfort of the patients in the postoperative period, and enabled the surgeons to look through the fundus during follow-up. The patients were less anxious about visual acuity after operation because those who had PPV plus gas tamponade could
see nothing until the gas was absorbed. The technique of glue application is easy and can be mastered quickly.

A major limitation of this study was the number of patients, as it was not a multicenter study. Further studies are required to assess the long-term safety and complications of fibrin glue.

**Key words:** fibrin glue, rhegmatogenous retinal detachment, par plana vitrectomy.

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