Comparison of Sutures and Cyanoacrylate Tissue Adhesives for Wound Repair in a Rat Model of Corneal Laceration

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Abstract
Aims: The aim of the present study was to evaluate the cicatricular repair of a corneal artificial perforation in rats with 10-0 nylon suture, N-butyl-2-cyanoacrylate (NBCA) adhesive, or NBCA + methacryloxyisulfonate (NBCA-MS) adhesive through microscopic and histological assays. Methods: Twenty Wistar rats were randomly divided into 4 groups each containing 5 rats: (1) control group (corneal trauma without suturing and tissue adhesives), (2) suture group, (3) NBCA group and (4) NBCA-MS group. A central full-thickness 2-mm laceration was performed in the left eyes of the studied rats in all 4 groups. The presence of corneal edema, corneal neovascularization and tissue adhesive/suture were evaluated. On the 21st day, the rats were sacrificed and histological examination was performed to determine irregularity of corneal layers, superficial epithelization, polymorphonuclear leucocytes and neovascularization. Results: Tissue adhesives were as effective as suturing in closing full-thickness corneal wounds and no difference in postoperative healing was observed clinically. As for the histological results, suture-treated eyes had persistent corneal irregularity that can limit visual acuity and may also lead to astigmatism. Conclusions: The use of tissue adhesives constitutes a viable alternative clinical procedure to conventional sutures. Possible influences on astigmatism are hypothetical, as no objective measure of astigmatism was performed in the test animals.
traction through hydrogen bonding and general attraction of masses or van der Waal forces. Different types of cyanoacrylate adhesive have been used in surgery. They can only be used externally because they induce inflammation. The tensile strength is one of the highest of all tissue glues. Cyanoacrylate corneal adhesives have traditionally been the most widely used glues for ophthalmic surgery [3]. N-butyl-2-cyanoacrylate (NBCA) (Glubranh 1; GEM s.r.l., Viareggio, Italy) is a cyanoacrylate glue used in surgery, digestive tract endoscopy, and arterial and venous embolizations [4]. NBCA + methacryloxy sulfolane (NBCA-MS; Glubran 2; GEM s.r.l.) is a new cyanoacrylate glue with a longer radical chain and with the same therapeutic applications as NBCA. Experimental studies have shown that equivalent cast homogeneity can be achieved by both NBCA and NBCA-MS in vessels but that NBCA-MS has a lower temperature of polymerization than NBCA, resulting in a lower histotoxicity and less inflammatory reaction [5].

The aim of the present study was to evaluate the tricial repair of a corneal artificial perforation in rats and its alternative repair with 10-0 nylon suture, NBCA adhesive, or NBCA-MS adhesive through slit lamp microscopy and histological assays in a rat model.

Methods

Study Design

The study was approved by the Ethics Committee on Animal Experimentation of our institution (protocol No. 2005/26). All procedures were performed in accordance with ethical standards laid down in the Declaration of Helsinki. Twenty healthy male Wistar rats weighing about 200–250 g were used for the study. The animals were kept in appropriate animal facilities under controlled conditions throughout the experiment, with free access to food and water. All animals received humane care. All animals underwent a baseline ocular examination to rule out preexisting anterior segment abnormalities. All surgical interventions were performed under sterile conditions by the same surgical team. All surgical interventions were performed in accordance with ethical standards of the adhesive-treated or sutured eyes. All other eyes

Outcome Measures

Eyes were examined on postoperative days 3, 10 and 21. Evaluation of blepharospasm was performed before the induction of general anesthesia. In the evaluation, scores 0 and 1 indicated the absence and presence of blepharospasm, respectively. During ophthalmological examination performed under general anesthesia using a biomicroscope (10×), the presence of corneal edema, corneal neovascularization and tissue adhesive/suture were evaluated. Seidel positivity was also checked to ensure that wounds were not self-sealing.

On the 21st day, all rats were sacrificed by an excessive dose of pentobarbital sodium (100 mg/kg i.p.). Cornea materials of all groups were placed separately into 10% neutral-buffered formalin. Fixed globes were bisected at the level of the surgical site and dehydrated in a series of graded alcohol prior to embedding in paraffin. Sections of 2-μm thickness were stained with hematoxylin and eosin (HE) for histopathological observations. Masked histological examination was performed to determine the extent of corneal healing, although the use of sutures prevented true masking of histological observations. A 4-point (0–3) grading system was used to record findings of various oculocutaneous reactions according to their severity: 0 = absent, 1 = mild, 2 = moderate and 3 = severe. Scores were assigned to 4 variables: irregularity of corneal layers, superficial epithelization, the presence of polymorphonuclear leukocytes, and the degree of neovascularization.

Statistical Analysis

Data were analyzed using the SPSS software (version 13.0 for Windows). All differences associated with a chance probability of ≤0.05 were considered statistically significant. Associations between categorical variables were analyzed by the Mann-Whitney test and the Kruskal-Wallis test.

Results

Among the 20 rats which we included in the study groups, only 1 rat (in the NBCA-MS applied group) died and was excluded from the study. During the study period, no complication (e.g. endophthalmitis) which would affect the study was seen in any rat.

Clinical Results

Seidel testing showed slight leakage immediately after closure in 1 of the eyes in the control group and in none of the adhesive-treated or sutured eyes. All other eyes
were Seidel negative and all anterior chambers remained formed (table 1). Ophthalmological examination of the rats on postoperative day 3 showed the incidence of blepharospasm and corneal neovascularization in group 1 (control group) to be significantly lower (p < 0.05). No difference was seen between groups for corneal edema (table 1). Ophthalmological examination of the rats on postoperative day 10 showed the incidence of corneal neovascularization to be significantly lower in group 1 (p < 0.05). No difference was seen between groups for blepharospasm, corneal edema and Seidel positivity. On postoperative day 21 no difference between groups was observed in the ophthalmological examination of rats.

**Histological Results**

After completion of ophthalmological examinations on postoperative day 21, the rats were sacrificed, and their eyes were examined histopathologically (table 2). A statistically significant difference existed between groups for superficial epithelization (p = 0.025), irregularities in corneal layers (p = 0.004), neovascularization (p = 0.006) and polymorphonuclear leucocytes (p = 0.003). Group 1 (control group) had the most normal histopathological results, and a significant difference between groups 3 and 4 was not detected, while in group 2, the number of abnormal histopathological findings was found to be significantly higher (p < 0.05). In group 1, the wound healing process was observed to be normal. Compared with the control group, higher rates of macrophage migration, neovascularization, and corneal irregularities were observed in group 2. In this group superficial epithelization was more marked with active healing. Although groups 3 and 4 had similar healing processes relative to group 2, lower rates of neovascularization in groups 3 and 4 were observed. Superficial epithelization and corneal layers in groups 3 and 4 were relatively more regular. Corneas that had been repaired with adhesives had better wound closure compared with corneas repaired with sutures, with a much more regular anterior surface of the cornea. There was no clinical or histological evidence of epithelial downgrowth in either group. For all histological findings, see figures 1–4.

**Discussion**

Corneal wound healing studies have been performed on primates, cats, dogs, rats, chickens and rabbits [6–10]. Of these animal models, the primate eye is generally accepted as the most similar to the human eye [11]. However, these earlier in vivo experiments did not justify the use of such a primate model. In the present study, we chose the rat (Wistar) model for investigation.

Although both suturing and adhesive repair of corneal lacerations can be effective, each has significant drawbacks. Limitations of sutures are as follows: first,
suture placement itself inflicts trauma on corneal tissues, especially when multiple passes are necessary. Second, suture material may incite infection, inflammation and vascularization [12]. Third, asymmetric healing and high levels of astigmatism may arise because of uneven tension on sutures [13]. The postoperative integrity of the sutures may also be problematic, with suture loosening or breaking requiring timely removal. Loose sutures may also harbor bacteria and cause local inflammation and tissue necrosis as a prelude to infection and possibly endophthalmitis. Last, suturing often entails prolonged surgical time and surgical skill, especially in the presence of extensive injuries. To avoid these disadvantages, ophthalmic surgeons are switching to sutureless surgery. A number of recent developments have established tissue adhesives as attractive alternatives to sutures.

Despite recent advances in tissue adhesives, the search for ideal biological glue continues. Cyanoacrylate tissue
adhesives were first used in the 1960s by Webster et al. [14] in the repair of corneal perforations. These adhesives are an effective therapeutic option in the treatment of small corneal perforations and in the prophylactic treatment of progressive corneal thinning disorders [15]. Cyanoacrylate corneal adhesives also have limitations with regard to their ease of applicability and effectiveness [16]. The technique requires adept and delicate application of a precise amount of adhesive in a dry environment to facilitate wound closure. Therapeutic effectiveness is often restricted to small corneal perforations of usually less than 1–2 mm because of inability to close larger perforations. Patients can experience discomfort from this material in the eye and, thus, a bandage contact lens is often used. Furthermore, cyanoacrylate adhesives may become opaque when they polymerize, thus obscuring the view of the underlying structures [17].

Tissue adhesives have been successfully used as a hemostatic and adhesive adjunct in many types of surgeries, including cardiovascular, thoracic, gastrointestinal, neurosurgical, urological, otolaryngological and orthopedic surgeries [18, 19]. Many studies of ophthalmic applications have recently been published [20]. Marticorena et al. [21] applied tissue adhesive for closing conjunctival autograft in primary pterygium surgery. They reported that the use of tissue adhesive reduced the foreign body sensation and the time of surgery because of its fast and easy application. Uy et al. [22] compared tissue adhesive and 10-0 nylon sutures and found significantly less postoperative discomfort and shorter surgical time in the fibrin glue group than in the suture group. No serious complications developed in their study. Kortoniy et al. [23] showed in their study that tissue adhesives decreased surgical time and patient discomfort markedly compared with the use of 7-0 vicryl rapid suture materials in pterygium surgery. In view of these studies, tissue glue is superior to suture material in accelerating postoperative recovery.

There have been histopathological studies concerning the absent toxic effect of tissue adhesives on ocular tissue [24–26]. Furthermore, the application of cyanoacrylate glue is difficult because it immediately solidifies on contact with water and can cause complications such as cataract, corneal infiltrates, keratitis, glaucoma and retinal toxic effects [26]. In the present study, tissue adhesives caused mild inflammatory reaction and had no observed adverse effect on ocular tissue. The application of tissue adhesives was as effective as traditional suturing in closing full-thickness corneal wounds, and no difference in postoperative healing between the groups was observed clinically. However, for the histological results, some differences in the healing response deserve mention. Suture-treated eyes had persistent corneal irregularity that can limit visual acuity and may also lead to astigmatism. Possible influences on astigmatism are hypothetical, as no objective measure of astigmatism was performed in the test animals.

Although our results are not strictly comparable to those in other experimental models using different bioadhesives, we were able to demonstrate a superior sealing effect of the cyanoacrylate tissue adhesives compared with standard suturing.

In the present study, even though tissue adhesives were seen to be more effective relative to suture materials in the healing process of corneal incisions, histopathologically corneal incisions left to spontaneous healing demonstrated the most satisfactory healing. In conclusion, the use of tissue adhesives to repair a corneal wound constitutes a viable alternative clinical procedure to conventional sutures and, thus, surgical time decreases, postoperative comfort improves, and suture-related problems can be avoided.

**Disclosure Statement**

None.

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**References**