

# A Comparison of 2-Octyl Cyanoacrylate Adhesives versus Conventional Suture Materials for Eyelid Wound Closure in Rabbits

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**Purpose:** To evaluate the clinical efficacy and histopathological tolerance of 2-octyl cyanoacrylate versus conventional suture materials for eyelid wound closure in rabbits.

**Methods:** We performed an experimental study on 16 eyes of eight New Zealand albino rabbits. Eyelid incisions of 15 mm were done 4mm from the upper eyelid margin in both eyes. The eyes of the rabbits were divided into two groups: eyelid incisions of the right eye were closed by a 2-octyl cyanoacrylate adhesive (group A) and eyelid incisions of the left eye were closed by 7-0 nylon sutures (group B). At 1, 2, 4, and 8 weeks after surgery, the rabbits were macroscopically examined and then sacrificed. The specimens of their eyelid tissues were stained by a hematoxylin and eosin stain and Masson-trichrome stain, and were observed under microscope.

**Results:** Both eyelid surgical closure methods were found to be equally efficacious in fixing the eyelids of groups A and B, and their clinical efficacy was similar. Histopathological findings of the hematoxylin and eosin stain of group A showed less inflammatory infiltration than group B at 2 weeks. There were no significant histopathological differences between the two groups at 1, 4, and 8 weeks. The degree of fibrosis of the Masson-trichrome stain was similar between the two groups at 8 weeks.

**Conclusions:** The 2-octyl cyanoacrylate adhesive proved to be an effective eyelid closure method and was very well tolerated by the skin surface. 2-Octyl cyanoacrylate could be used as an alternative tissue adhesive for eyelid wound closure along with conventional suture materials.

**Key Words:** Eyelid wound closure, Octyl 2-cyanoacrylate

Eyelid closure is often needed after various oculoplastic surgeries due to eyelid lacerations by trauma and blepharoplasty. The eyelid closure method using conventional suture materials can cause pain to patients from temporary edema after surgery, outpatient revisits for the removal of suture materials, and hyperemia and inflammation due to the suture material. In addition, eyelid closure using suture materials can cause various complications after surgery such as inflammation, irritation, foreign body sensation, and granuloma formation. The cyanoacrylate adhesive has suitable features for wound

closure such as proper strength, tissue barrier capability, flexible binding, and binding ability in moist environments [1]. However, the cyanoacrylate adhesive that was used for eye surgery before had several shortcomings such as severe toxicity to biological tissues, low biodegradation capacity, and severe intraocular irritation [2-4]. In particular, formaldehyde that was generated during its biodegradation had toxicity to biological tissues, and could cause acute and chronic inflammation. According to findings from many previous studies, the longer the chain length of the cyanoacrylate derivative, the lower its toxicity. Various tissue adhesives that were commercially used before had short-chain derivatives and caused initial acute inflammation and chronic foreign body reactions [5,6].

2-Octyl cyanoacrylate (Dermabond; Ethicon Inc., Somerville, NJ, USA), which was certified by the U.S. Food and Drug

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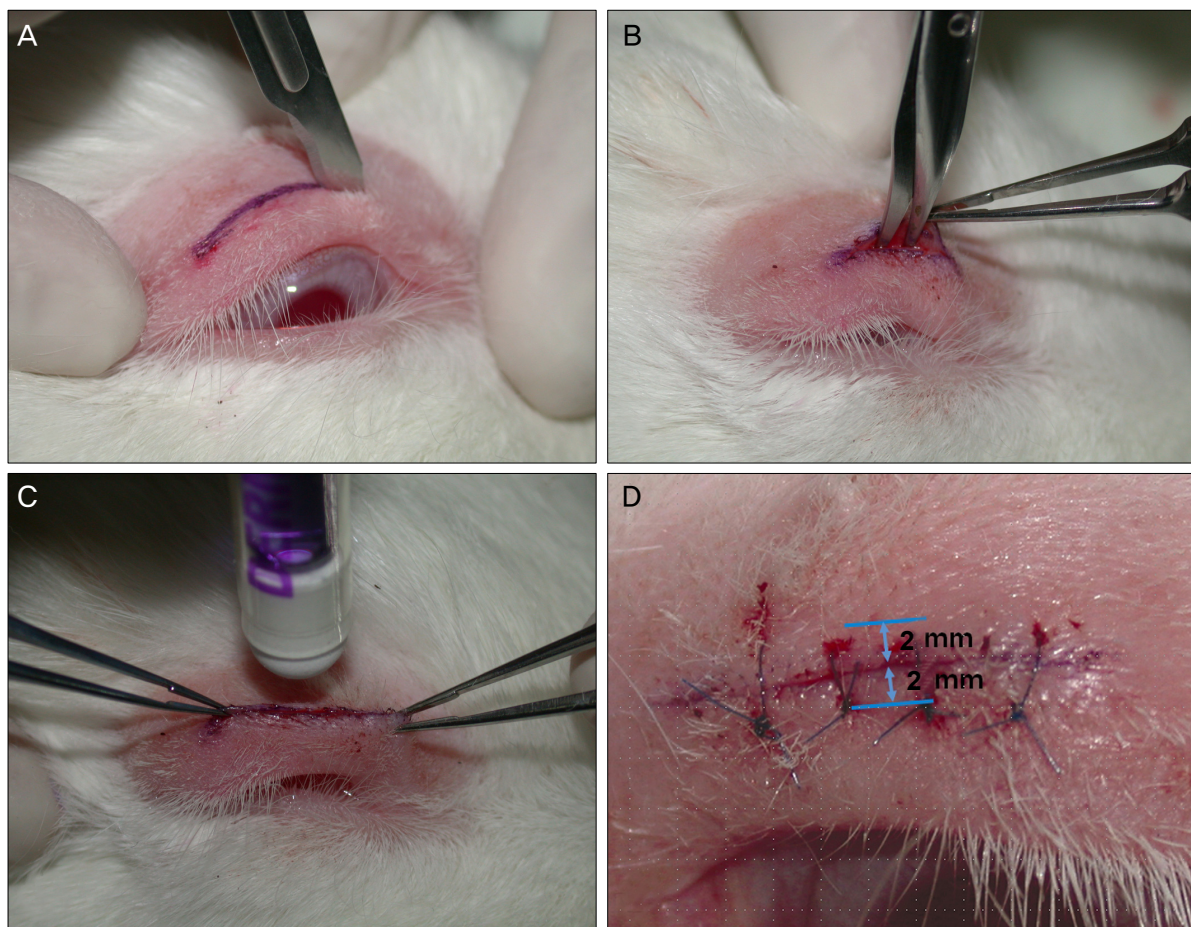
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Administration in 1998, was developed for use in external wounds. Because it is a longer-chain derivative, it is slowly degraded in vivo. Therefore, it results in milder acute or chronic inflammation, clean absorption, and fewer tissue necroses [5]. In addition, because its flexibility is better than conventional cyanoacrylate, it can also be used on irregular surfaces as well [7]. Thanks to these benefits, the longer-chain derivative 2-octyl cyanoacrylate is now being used for treatment of skin lacerations of young patients, and is being researched and universally used as a new alternative closure method [7-9]. Accordingly, through this study, the authors wanted to investigate the clinical effects and biocompatibility of the 2-octyl cyanoacrylate tissue adhesive, a longer-chain derivative with lesser toxicity to tissue than conventional cyanoacrylate, through a comparison with conventional 7/0 nylon non-absorbable suture materials to examine the possibility of applying 2-octyl cyanoacrylate adhesives to oculo-plastic and other ophthalmic areas.

## Materials and Methods

### Surgical method

The subjects in this study consisted of 16 eyes of eight New Zealand albino rabbits with weights ranging from 2-3 kg. For anesthesia, 50 mg each of ketamine hydrochloride and xylazine hydrochloride were injected into the muscles of the laboratory animals. The area around the upper eyelids of both eyes of the anesthetized rabbits was shaved to expose their skins, and a 15 mm skin incision was completed 4 mm from each eyelid margin (Fig. 1A). The epidermis was dissected and the tarsal plate was exposed to artificially bring about a condition that was similar to an actual blepharoplasty (Fig. 1B). The eyes of the rabbits were divided into two groups: eyelid incisions of the right eyes were closed by a 2-octyl cyanoacrylate adhesive (group A) and eyelid incisions of the left eye were attached again by 7-0 nylon sutures (group B) (Fig. 1C and 1D). After surgery, a tobramycin ophthalmic ointment was applied to the eyelids of the rabbits



**Fig. 1.** Surgical technique. (A) A eyelid incision of approximately 15 mm was made. (B) The incision was blotted dry using cotton swabs. Subcutaneous tissue was dissected with the use of Wescott scissors. (C) In group A, a thin layer of 2-octylcyanoacrylate was applied along the edges of the incision. (D) In group B, 7-0 nylon sutures were used in the form of stitches that fixed the edges of the eyelid. Full-thickness biopsies including 2 mm above and below the the incision site were taken for blinded histopathological evaluation. In group A, full-thickness biopsies were also taken by the same method.



twice a day, and 80 mg of gentamicin was injected into the muscle.

### Macroscopic and histological examination

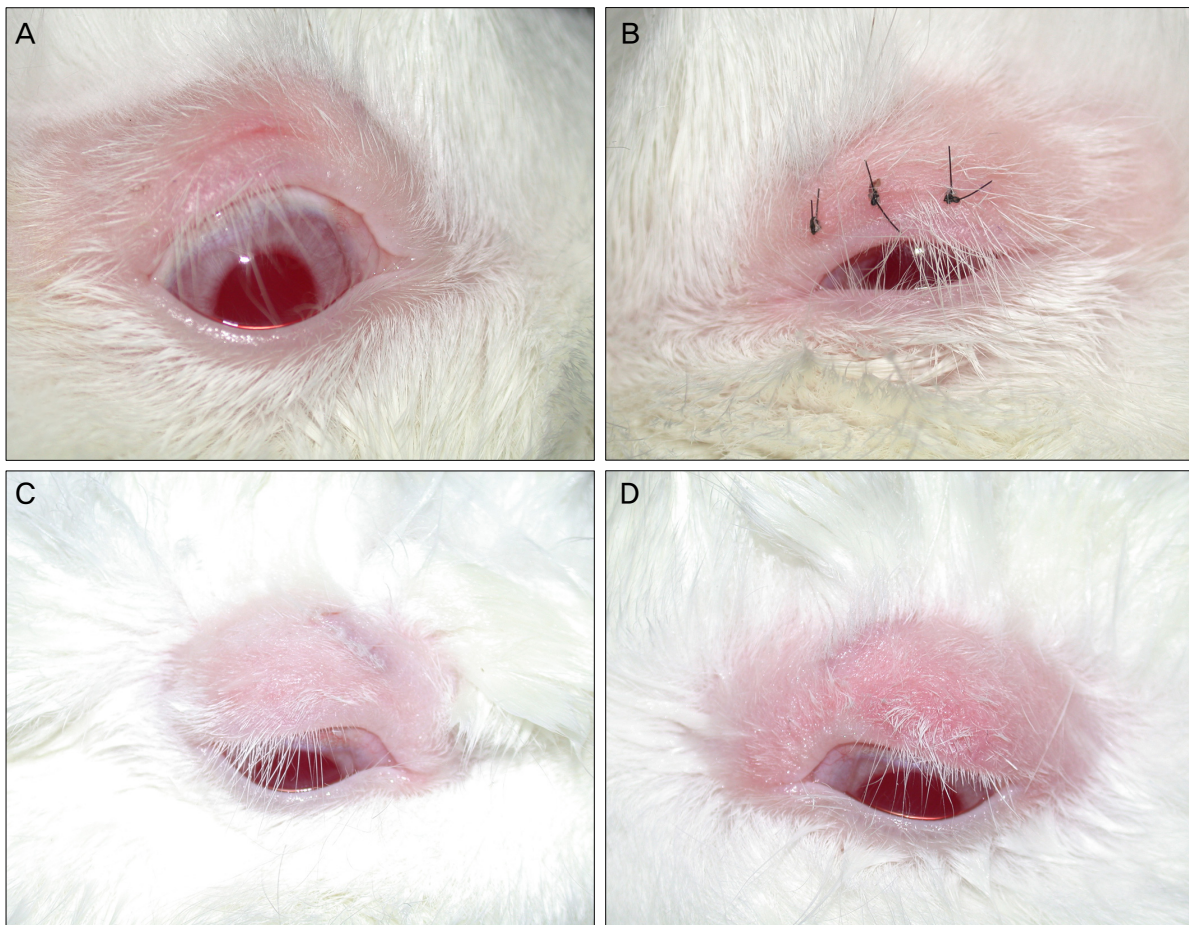
At 1, 2, 4, and 8 weeks after surgery, the operated regions of the upper eyelids of the rabbits were macroscopically examined for edema, flare, degree of traction by skin adhesion, and other changes. To examine the curing process of the tissues and compare the tissue reactions between the two groups, two rabbits were sacrificed every 1, 2, 4, and 8 weeks. Full-thickness biopsies including 2 mm above and beneath the incision sites were taken for blinded histopathological evaluation by a board-certified pathologist (Fig. 1D). Each tissue specimen was fixed in 10% buffered formalin to create a tissue slice. To observe inflammatory cell infiltration, hematoxylin and eosin (H&E) staining was performed and the stained tissues were observed under an optical microscope. The degree of inflammatory cell infiltration was semi-quantitatively analyzed and was classified into mild, moderate, and severe. To examine the degree of fibrosis by collagen synthesis, Masson-trichrome staining was conducted and the

specimens were observed under a microscope ( $\times 40$ ) for comparison of the two groups.

## Results

### Macroscopic findings

Comparison of the 16 eyes of eight rabbits found that the wounds were effectively conjugated in both groups A and B throughout the entire period. Right after surgery, it appeared that tractive force in the eyelids of group A caused wrinkles. However, when we compared the locations and forms of the eyelids one week after surgery, no differences were found between the two groups. One day after surgery, slight edema in the eyelids was observed only in group B, and no secretion was observed in either group. Four days after surgery, the edema and flare of the eyelids disappeared in both groups, and the wounds were effectively cured without complications such as infections or wound dehiscence. One week after surgery, the suture materials were removed from group B. Two weeks after surgery, no differences between the two groups could be seen by macroscopic examination (Fig. 2C



**Fig. 2.** Macroscopic aspect of specimens. Macroscopic aspect of specimens treated with 2-octylcyanoacrylate (A, 1 week; C, 2 weeks) and 7-0 nylon sutures (B, 1 week; D, 2 weeks).



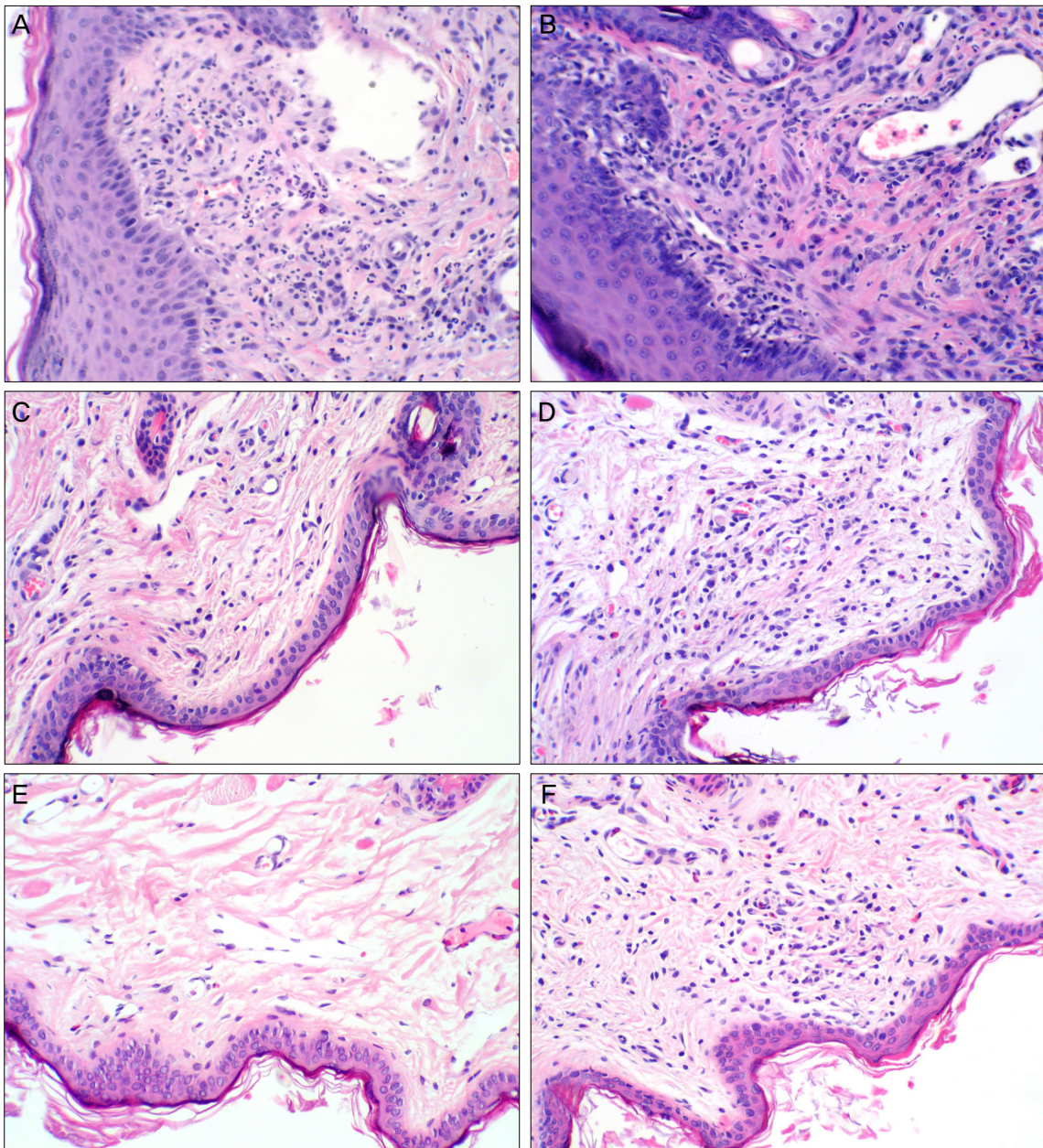
and 2D). After adhesion and suture of the incisions, no complications such as wound dehiscence, granulomas, and hematomas were observed in either group.

### Results of histopathological observations

#### 1) Hematoxylin and eosin staining

One week after surgery, adhesive materials on the surface,

minor infiltration of inflammatory cells, and proliferation of fibroblasts were observed in group A. In group B, minor acute inflammatory cells and proliferation of fibroblasts were observed around the suture material. Most inflammatory cells were monomorphonuclear cells (Fig. 3A and 3B). Two weeks after surgery, moderate inflammation was found in group B while minor inflammation was found in group A. Therefore, group A was found to have less inflammatory



**Fig. 3.** Histological findings of the incised eyelid (hematoxylin and eosin stain,  $\times 200$ ). (A) The eyelid at 1 week of group A exhibits mild to moderate acute inflammatory cell infiltration and mild to moderate fibroblastic proliferation. (B) The eyelid at 1 week of group B shows moderate acute inflammatory cell infiltration and mild to moderate fibroblastic proliferation and foreign body reaction. (C) The eyelid at 4 weeks of group A shows mild inflammatory cell infiltration. (D) The eyelid at 4 weeks of group B shows mild eosinophilic infiltration. (E) The eyelid at 8 weeks of group A shows nearly normalized morphology with very mild inflammatory cells and fibroblasts. (F) The eyelid at 8 weeks of group B shows mild foreign body inflammatory reaction with the presence of eosinophils.



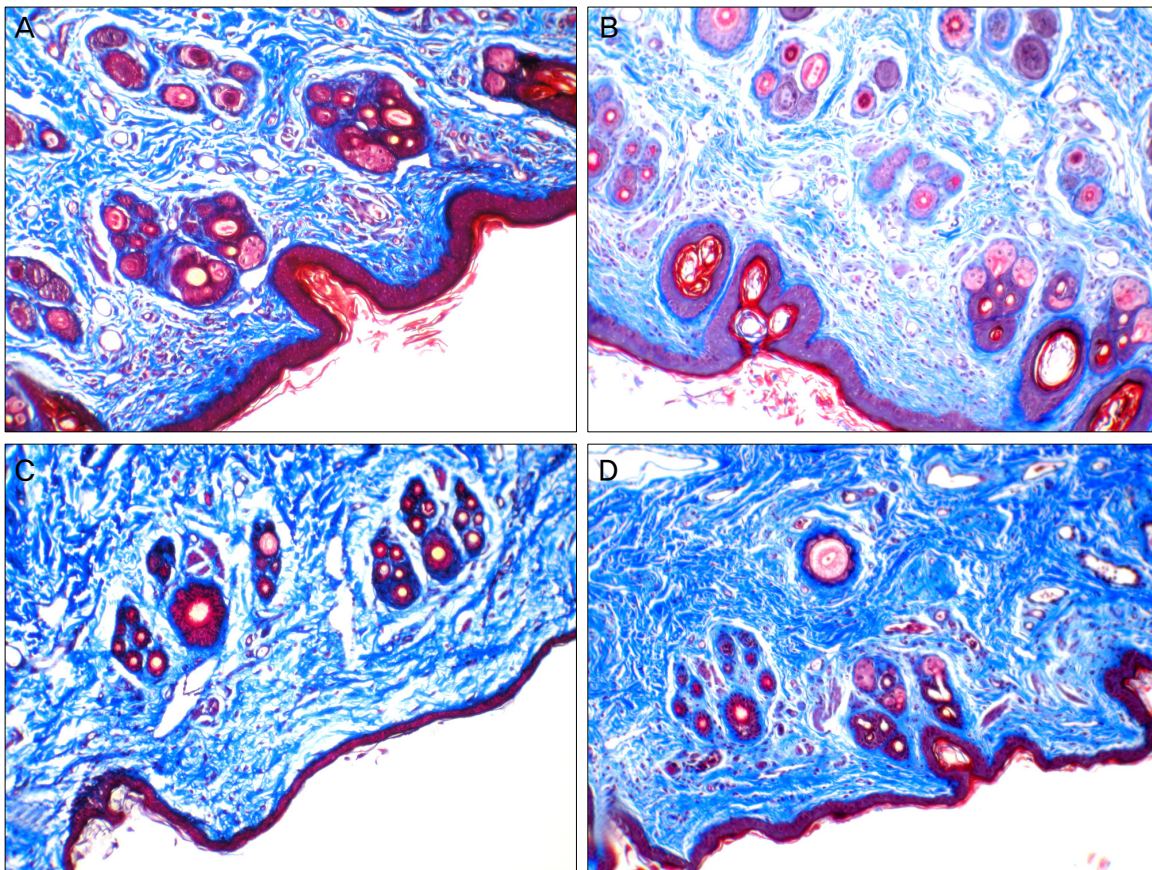
reactions. Four weeks after surgery, the concentration of inflammatory cells and fibroblasts decreased in group A, while foreign body and inflammatory reactions continued in group B (Fig. 3C and 3D). Eight weeks after surgery, inflammatory cells almost disappeared in group A, while mild foreign body inflammatory reactions remained in group B (Fig. 3E and 3F). These findings confirmed that eyelid closure using nylon causes inflammatory and foreign body reactions for a considerable length of time. However, considering the diverse degrees of inflammation according to the quantity of adhesive used and the small number of specimens, it was difficult to accurately determine which group had more or less severe inflammation after surgery.

## 2) Masson-trichrome staining

Masson-trichrome staining turned muscular tissues red. The fibrous tissues between the tarsal plate and orbicularis oculi muscle as well as the inner subcutaneous tissues were stained deep blue. At week one, the Masson-trichrome staining found that group A exhibited almost normal fibrosis while mild edema was found in group B. At eight weeks, the overall fibrosis showed no difference between the two groups (Fig. 4).

## Discussion

Until now the cyanoacrylate tissue adhesive could be easily used for eyelid closure after face reconstruction or other ophthalmic surgeries due to its benefits such as even strength and flexible binding which are appropriate for closure, tissue barrier capability, and short action time [10-13]. Even though the adhesive that was first tried in biological tissues was methyl-2 cyanoacrylate, it was replaced with n-butyl cyanoacrylate due to excessive biological toxicity [12,14]. When n-butyl cyanoacrylate was used in corneal tissue, necrosis of corneal solid tissue, giant papillary conjunctivitis, granulomatous keratitis, and excessive irritation were reported [12,15]. Tissue adhesive materials must have flexibility, be able to cover the entire eyelid wound region to prevent complications such as bacterial infection, and have no complications such as epithelial defects or necrosis of tissues due to toxicity. 2-Octyl cyanoacrylate that was used for this experimental study is a recently developed longer-chain derivative that did not show any inflammation or toxic effects through optical microscopic examination except for early inflammation and foreign body reaction after surgery. Furthermore, the adhesive materials were quickly absorbed



**Fig. 4.** Histological findings of fibrosis (Masson-trichrome stain,  $\times 100$ ). (A) The eyelid at 1 week show nearly normalized fibrosis in group A. (B) The eyelid at 1 week show slightly edematous change in group B. The eyelid at 8 weeks show similar findings in group A (C) and group B (D). Mild fibrosis with deposition of collagen is seen.

and no clinical complications such as epithelial defects or necrosis of tissues were found.

The 2-octyl cyanoacrylate tissue adhesive is a disposable violet liquid with low viscosity that spreads thinly and exhibits the strongest binding when it is polymerized [16]. Ten to fifteen seconds after polymerization, semitransparent glue material covers the wound region. At this time, care must be taken so that the adhesive material will not run sideways from the eyelid and adhere to other surrounding tissue. In one case during this experimental study, some residue of the 2-octyl cyanoacrylate adhesive remained on the eyelids until one week after surgery. The reason for this seems to be the excessive discharge of 2-octyl cyanoacrylate from its container during the wound closing process which remained on the eyelid. A new convenient container that can be used more easily in ophthalmic surgery is needed to prevent this from occurring.

The cell toxicity of cyanoacrylate is known to be related to the number of carbon atoms of the lateral chain in molecular structure [17-19]. Ethyl cyanoacrylate that has three carbon atoms has lower toxicity than methyl with two carbon atoms, but has a higher toxicity than butyl with four carbon atoms [20]. This study found that octyl cyanoacrylate with eight carbon atoms is a longer chain derivative than conventional cyanoacrylate, very slowly decomposes in vivo, shows a mild level of inflammation, and has lower toxicity.

2-Octyl cyanoacrylate has been evaluated in animals for the treatment of contaminated surgical incisions, burns, abrasions, excisional wounds, split thickness skin grafting, arterial repair, and middle ear surgery. A study by Quinn et al. [21] evaluated the clinical and histological infection rates in incisions in guinea pigs deliberately contaminated with *Staphylococcus aureus* closed with 2-octyl cyanoacrylate or sutures. While most sutured wounds became infected (65%), the infection rates were significantly reduced in 2-octyl cyanoacrylate treated wounds (20%,  $p < 0.01$ ). These results are not surprising since the cyanoacrylates have been found to have antibacterial effects when standard disk sensitivities have been used, especially against gram-positive bacteria [22].

Quinn et al. [23] evaluated the effects of a 2-octyl cyanoacrylate spray on the healing of superficial traumatic abrasions (down to the dermis) in guinea pigs. There were no differences in the healing of wounds treated with 2-octyl cyanoacrylate or Biobrane. A slightly different 2-octyl cyanoacrylate formulation applied with an activated porous applicator was evaluated by Davis et al. [24] in pigs with superficial (0.3 mm), small, and partial thickness excisional wounds. They found that wounds treated with 2-octyl cyanoacrylate re-epithelialized more rapidly than those treated with a hydrocolloid dressing, a standard bandage, or dry air exposure (63% vs. 30%, 20%, and 23%, respectively, on day 5). They also found that only 2-octyl cyanoacrylate provided complete hemostasis, reduced scab formation, and did not induce an irritant response or infection. Singer et al. [25] evaluated a

stronger 2-octyl cyanoacrylate formulation for the treatment of larger and deeper (0.6 mm) excisional wounds in swine. They found that the rates of re-epithelialization of 2-octyl cyanoacrylate treated wounds were similar to wounds treated with hydrocolloid and better than those treated with dry gauze. Interestingly, foreign body tissue reactions were least common in 2-octyl cyanoacrylate treated wounds. Also, 2-octyl cyanoacrylate was the only agent resulting in complete hemostasis. The 2-octyl cyanoacrylate dressing also demonstrated a microbial barrier function when challenged with *Staphylococcus aureus*.

As a result of the use of 2-octyl cyanoacrylate in this study, the incision was well attached throughout the entire period of the experiment, and no wound dehiscence or tissue necrosis was seen. 2-Octyl cyanoacrylate also showed similar clinical effects and efficacies as the conventional closure method. Therefore, we believe that 2-octyl cyanoacrylate can be used as an alternative to conventional suture materials. Furthermore, because 2-octyl cyanoacrylate has low toxicity and post-operative inflammation, it could be useful for eyelid and other ophthalmic surgeries. Additional clinical experiments and studies on its uses in other ophthalmic surgeries are necessary.

## Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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