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The effects of topical application of Octyl-2-cyanoacrylate tissue glue on the wound healing in mice: An experimental study

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Abstract

Objective

Management of patients with full thickness wound of skin continues to challenge physicians and surgeons in area of cosmetic dermatologic surgery. At the present time, there are some medications and procedures that can be used to accelerate the healing of full thickness wound of skin. Based on studies that have demonstrated improved upper eyelid wound healing with OCA (octyl-2-cyanoacrylate tissue glue) treatment, we anticipated that OCA will accelerate healing of full thickness wound of skin. The aim of research is to evaluate the efficacy of OCA in accelerating healing of full thickness wound of skin in mice.

Materials and Methods

Design: experimental study, Animals: Male N. mRi mice, Sample size: 6 per study group.
Surgery: two mm full thickness wound of skin back of mice under general anaestesia.
Treatment groups: Control group: simple dressing with sterile guaze, OCA group: topical application octyl-2-cyanoacrylate (Dermabond; Ethicon Inc, Somerville, NJ) tissue glue.
Study Period: mice were euthanized on days 4, 7 and 10 post-operation to reflect different phases of wound healing, Assay: 1- gross pathology of the skin noting presence of infections, dehiscence and repair, 2- histological evaluation of the wound site for the degree of healing, 3-finally the wounds were tested for, Resilience = ability of the wound to stretch and then resume shape without incurring any tissue damage, ultimate strength = maximum pressure a wound can tolerate before it starts to weaken and toughness = total amount of pressure a wound can tolerate before rupturing.

Results

OCA increased: 1) formation of granulation tissue 2) density and activation of fibroblasts 3) keratinization in surface of wound 4) thickness of basement membrane and epidermis. OCA decreased infection, inflammation, edema and dehiscence. Finally OCA increased resilience, ultimate strength and toughness of wound in mice.

Conclusion

We conclude that OCA accelerates healing of full thickness wound of skin in mice.

Key words: Mice, OCA, Resilience, Wound healing.

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Introduction

Maintaining skin integrity is vital for human and animals to protect the organism against dehydration, bleeding and ingress of microorganisms. In order to do this, animals evolved a sophisticated mechanism of wound healing to quickly plug the gap, re-epithelialize over the defect and rapidly replace the lost dermis with new matrix. Clearly, the speed of wound healing depends upon many factors, including the size of the wound, blood supply to the area, presence of foreign bodies and microorganisms, age and health of the patient, nutritional status of the patient (1).

Management of patients with full thickness wound of skin continues to challenge physicians and surgeons in area of cosmetic dermatological surgery. At the present time, there are some medications and procedures that can be used to accelerate the healing of full thickness wound of the skin.

Based on studies that have demonstrated improved wound healing with OCA (octyl-2-cyanoacrylate tissue glue) treatment, (2-5) we anticipated that OCA will accelerate healing of full thickness wound of skin. It is evident from preliminary data, that OCA may be an effective, simple, non painfull (unlike suture) and safe therapeutic agent for accelerating wound healing.

Materials and Methods

Design: Prospective, randomized, blinded experimental study comparing cosmetic and functional outcome, *Animals:* Male N.mRi mice, *Sample size:* 6 per study group, *Surgery:* Two mm full thickness wound of skin in back of mice under general anaestesia, *Treatment groups:* Control group: simple dressing, OCA group: topical application octyl-2-cyanoacrylate (Dermabond; Ethicon Inc, Somerville, NJ) tissue glue. The edges of wounds to which OCA was applied were approximated. We painted the OCA over the opposed wound edges with the applicator tip and were careful not to apply adhesive between the wound edges (If OCA is applied in the deeper part of a wound, between the wound edges, it acts as a foreign body and as a barrier to wound healing). The wound was held for 30 seconds to allow complete polymerization. No dressing is required.

Study Period: Mice (2 mice were selected at the each days of examination) were killed with an overdose of anesthetic on days 4, 7 and 10 post-operation (to reflect different phases of wound healing) and then a piece of treated skin were removed and fixed with 10% neutral formalin solution. After fixation, routine processes of tissue preparation such as dehydration, clearing and infiltration were performed and specimens were embedded in paraffin. The paraffin blocks were trimmed and thin serial sections (3-5 micrometer) were cut with Ziess Rotary Microtome. Some sections were randomely selected and stained with Heamtoxilin and Eosin. A dermatologist and two pathologists that blinded about groups observed the sections and data were gathered and analysed.

Assay: 1- gross pathology of the skin noting presence of infections, dehiscence and repair, 2- histological evaluation of the wound site for degree of healing, 3- Finally the wounds were tested by a dermatologist for:

Resilience = ability of the wound to stretch and then resume shape without incurring any tissue damage, ultimate strength = maximum pressure a wound can tolerate before it start to weaken, and toughness = total amount of pressure a wound can tolerate before rupturing.

Results

Macroscopic features of wounds on day 4

1) OCA group: there was no dehiscence, infection and exudate respectively, but scab on surface of wounds was seen. The mean gap between two edges of wound was 0.2 mm. Surface of wounds was pinkish, swollen and warm but less than control group.

2) Control group: there was no infection, but exudate and scab on surface of wounds was seen. The mean gap between two edges of wound was 3 mm. Surface of wounds was

reddish, more swollen and warmer than OCA group.

Microscopic features of wounds on day 4

OCA versus control group increased: 1) formation of granulation tissue, 2) density and activation of fibroblasts, 3) keratinization on the surface of wound, 4) thickness of basal membrane and epidermis on day 4. OCA versus control group decreased inflammation, edema and dehiscence on day 4 (Table 1).

Degree of inflammation of wounds in control group was more than OCA group on day 4. Most of inflammatory cells of wounds in control group were polymorphonuclears (98%) and also most of inflammatory cells of wounds in OCA group were polymorphonuclears (75%) on day 4.

Macroscopic features of wounds on day 7

1) OCA group: there was no dehiscence, infection and exudate respectively, but scab on surface of wounds was seen but less than day 4. The mean gap between two edges of wound was 0.1 mm. Surface of wounds was pinkish, swollen and warm but lesser than day 4 and control group, 2) Control group: there was no infection and exudate respectively, but the scab on surface of wounds was seen. Mean gap between two edges of wound was 2 mm. Surface of wounds was reddish, more swollen and warmer than OCA group.

Microscopic features of wounds on day 7

OCA versus control group increased: 1) formation of granulation tissue , 2) density and activation of fibroblasts 3) keratinization in surface of wound 4) thickness of basal membrane and epidermis, 5) thickness of collagen fiber on day 7 (Table 2).

OCA versus control group decreased inflammation, edema and dehiscence on day 7.

Degree inflammation of wounds in control group was more than OCA group. Most of inflammatory cells of wounds in control group were lymphocyte (80%) and also most of inflammatory cells of wounds in OCA group were lymphocyte (95%) on day 7.

Macroscopic features of wounds on day 10:

1) OCA group: there was no dehiscence, infection, exudate and scar respectively. Surface of wounds was normal, 2) Control group: there was no infection and exudate respectively, but inflammation and scar was present. Surface of wounds was reddish but less than day 7.

Microscopic features of wounds on day 10

OCA versus control group increased: 1) density and activation of fibroblasts 2) keratinization in surface of wound 3) thickness of basement membrane and epidermis 4) thickness of collagen fiber on day 7 (Table 3).

Inflammation of wounds was absent in OCA group on day 10. Degree of inflammation of wounds in control group on day 10 was less than on day 7. Most of inflammatory cells of wounds in control group were lymphocyte (85%) on day 10. Finally OCA increased resilience, ultimate tensile strength and toughness of wound in mice.

Table 1: Microscopic features of wounds in two groups on day 4.

Parameters	Control group	OCA group
Inflammatory cells density	++++	+++
Inflammatory cells type	PMN (98%) Lymph (2%)	PMN (75%) Lymph (25%)
Granulation tissue formation	-	-/+
Edema	++	+/-
Fibroblasts density	-	+/-
Fibroblasts activation	-	+
Basal membrane	2-3 layer	3 layer
Increased thickness of epidermis in edge of wounds	7 layer	8 layer
Keratinization in surface of wounds	+ Parakeratotic	+ Ortho and parakeratotic

Table 2: Microscopic features of wounds in two groups on day 7.

Parameters	Control group	OCA group
Inflammatory cells density	++	+/-
Inflammatory cells type	PMN (20%) Lymph(80%)	PMN (5%) Lymph(95%)
Granulation tissue formation	++	+++
Collagen fiber density	+	++
Fibroblasts density	++	+++
Fibroblasts activation	++	++
Thickness of collagen fiber	30% of normal	40% of normal
Increased thickness of epidermis in edge of wounds	5 layer	6 layer
Keratinization in surface of wounds	++ Ortho and parakeratotic	+++ Orthokeratotic

Table 3: Microscopic features of wounds in two groups on day 10.

Parameters	Control group	OCA group
Inflammatory cells density	+	-
Inflammatory cells type	PMN (15%) Lymph(85%)	-
Granulation tissue formation	+/-	-
Collagen fiber density	+++	++++/+++
Fibroblasts density	+++	++
Fibroblasts activation	+++	++
Thickness of collagen fiber	50% of normal	60% of normal
Increased thickness of epidermis in edge of wounds	3 layer	3 layer
Keratinization in surface of wounds	+++ Ortho and parakeratotic	++ Orthokeratotic

Discussion

The cyanoacrylates first were synthesized in 1949 by Airdis (6). Coover et al. described their adhesive properties and suggested their possible use for surgical adhesives (7). In the early 1960s, various surgical applications were investigated for these adhesives.

Cyanoacrylates can be synthesized by reacting formaldehyde with alkyl cyanoacetate to obtain a prepolymer that, by heating, is depolymerized into a liquid monomer. The monomer then can be modified by altering the alkoxycarbonyl (-COOR) group of the molecule to obtain compounds of different chain lengths. Upon application to living tissues (water or base), the monomer undergoes an exothermic hydroxylation reaction that results in polymerization of the adhesive.

Until recently, butyl-2-cyanoacrylate was the only commercially available cyanoacrylate tissue adhesive. Although butyl-2-cyanoacrylate is effective in closing superficial lacerations under low tension, it has several limitations. Several studies have shown wound-breaking strength in wounds repaired with butyl-2-cyanoacrylate to be equal to that in wounds repaired with sutures at 5-7 days; however, on day 1, breaking strength with the tissue adhesive is only approximately 10-15% of that in a wound sutured with 5-0 monofilament. After polymerizing, the adhesive becomes brittle and is subject to fracturing when used in skin creases or long incisions. This restricts the use of adhesives to areas of low tension, thus limiting their use for incision repair. Butyl-2-cyanoacrylate has been used widely with

good cosmetic outcomes for various plastic surgical procedures (eg, upper lid blepharoplasty, facial skin closure, scalp wound closure).

The Food and Drug Administration (FDA) has approved 2-octyl cyanoacrylate for closure of incised skin. In addition to its surgical adhesive indication, 2-octyl cyanoacrylate (Dermabond) was approved by the FDA in January 2001 for use as a barrier against common bacterial microbes including certain staphylococci, pseudomonads, and Escherichia coli. Cost analysis has found that the use of tissue adhesives can significantly decrease health care costs and is preferred by patients. Adhesives also provide a needle-free method of wound closure, an important consideration because of blood-borne viruses (eg, HIV). The cyanoacrylates function as waterproof occlusive dressings, have antimicrobial properties against gram-positive organisms, and may decrease infections. They have been demonstrated to decrease histologic and clinical infection rates in contaminated wounds when compared to closure with sutures. If the adhesives are used improperly and are implanted into the wound, they can cause a foreign-body reaction and actually may increase infection rates.

The adhesive can be used topically to close skin incisions and lacerations alone, or it can be used in conjunction with deep sutures. Generally, the octyl products can be used in place of nonabsorbable sutures for primary closure of skin incisions and lacerations on the face. For facial incisions and lacerations that are under tension and when closing incisions and lacerations on the extremities and torso, deep (subcutaneous) sutures are recommended.

Toriumi et al. have published an excellent paper on the use of 2-octyl cyanoacrylate. They underscore two other important principles, which are the need to reduce skin tension at the site of the laceration and the need to ensure no dead space is present before sealing with the tissue adhesive (8).

Several clinical studies have shown that 2-octyl cyanoacrylate provides cosmetic results equal to those of sutures (9-13). Maw et al. compared the tissue adhesive octylcyanoacrylate with subcuticular suture for the closure of head and neck incisions. Fifty consecutive patients undergoing head and neck procedures at two University of Ottawa teaching hospitals. Twenty-six patients underwent skin closure with monofilament suture and 24 were closed with tissue adhesive. At 4 to 6 weeks the incisions were evaluated with a validated wound scale. Photographs of the incisions were rated using a visual analogue scale by two facial-plastic, otolaryngologists who were blinded to the method of skin closure. The adhesive provided faster skin closure (29.7 seconds vs 289.0 seconds, $p<0.0001$), and there were no differences in complications between the two groups. The primary outcome measure was the cosmetic appearance of the incision at 4 to 6 weeks. Although the adhesive group scored higher on both cosmesis scales, the visual analogue scale (octylcyanoacrylate 58.7 mm vs suture 53.2 mm) and the wound evaluation scale (57% vs 50% optimal wound scores), there were no statistical or clinically significant differences on either scale. The two facial-plastic otolaryngologists had good intraobserver and interobserver agreement when rating the cosmetic outcomes (0.87 and 0.71 respectively). Octylcyanoacrylate was found to be an effective method of skin closure in clean head and neck incisions (12). In this study we achieved excellent results in every case in terms of increased formation of granulation tissue, density and activation of fibroblasts, keratinization in surface of wound, thickness of epidermis and thickness of collagen fiber. These results corresponded with other studies (13-15). Recent studies suggest that the use of tissue adhesive for

closure of both traumatic lacerations and incisional surgical wounds leads to cosmetic outcome comparable to conventional sutures. Gennari et al. investigated tissue adhesive in breast surgery and costs. Their aim was to compare the tissue adhesive 2-octylcyanoacrylate (OCA) with standard suture in breast surgery. A prospective randomized study was conducted in which 151 patients were assessed for eligibility, and 133 were randomly allocated to skin closure with OCA adhesive or monofilament suture. Cosmetic outcome of blind assessment, wound management by the patients, complication rates, and economic outcome were recorded. There was no difference in cosmetic score in the 2 groups, nor in complications at the early, 6-months, and 1-year follow-up. Patient satisfaction with the wound closed with OCA was rated significantly higher when compared with standard suture ($p<0.0001$). The application of the tissue adhesive was significantly faster than that for standard suture ($p<0.001$). In economic terms total costs were less in the tissue adhesive group, mainly due to lower postoperative costs of physician and assistant services ($p<0.001$). OCA is effective and reliable in skin closure for breast surgery, yielding similar cosmetic results to standard suture. OCA is faster than standard wound closure and offers several practical advantages over suture repair for patients. Cost analysis has found that OCA adhesive can significantly decrease health care costs (14).

Our results have shown that OCA decreased infection, inflammation, edema and dehiscence. These results confirmed with other studies (16-20). Octylcyanoacrylate tissue adhesive is a topical wound closure that precludes the need for foreign bodies (sutures) to close wounds. It also has an *in vitro* antimicrobial effect when standard disc sensitivity tests are used. To determine whether contaminated wounds closed with octylcyanoacrylate tissue adhesive will have a lower infection rate compared with wounds closed with 5-0 monofilament sutures, Quinn et al. designed a randomized, blind, experimental animal study. Two incisions were made on 20 albino guinea pigs. The wounds were contaminated with 10^5 Staphylococcus aureus ATCC 12600 and randomly assigned to be closed with either topical octylcyanoacrylate tissue adhesive or percutaneous 5-0 polypropylene suture. Five days later the adhesive and sutures were removed, and a section of the wound was given to a histopathologist blinded to the type of wound closure. The wound was determined to be infected if inflammatory cells with intracellular cocci were seen. The rest of the wound was opened and examined for clinical evidence of infection. Quantitative bacteriologic analysis was performed. Five wounds in the tissue adhesive group were sterile on day 5, where as all sutured wounds had positive cultures (25% versus 0%, $p<0.05$). Fewer wounds in the tissue adhesive group were determined to be infected by histologic and clinical criteria (0% versus 55%, $p < 0.001$, and 20% versus 65%, $p<0.01$, respectively). Agreement on the determination of infection by histologic and clinical criteria yielded a kappa coefficient of 0.46 (95% confidence interval [GI], 0.19 to 0.73). An infection criterion of 10^5 colony-forming units/gm of tissue correlated poorly with clinical and histologic infection rates (0.19 [95% CI, -0.06 to 0.44] and 0.13 [95% CI, -0.05 to 0.31], respectively). Contaminated wounds closed with sutures had higher infection rates compared with those reported with topical tissue adhesive. The amount of colonization may not be an accurate method to determine infection (16).

Our findings have shown that the rapidity of healing seen with OCA topical application is noted. This finding confirm previous work (21-23). Yaron et al. compared the efficacy of

butyl-2-cyanoacrylate tissue glue (TG) for the repair of skin lacerations in rats with the efficacy of standard closure with sutures. In a prospective study, eight rats were anesthetized and an 8-cm dorsal incision was made on each side of the midline. One wound was closed with a single layer of interrupted 5-0 Prolene suture and one by application of TG. The time required to close each wound was recorded. Sutures were removed at seven days; the TG was allowed to fall off spontaneously. The animals were sacrificed after 20 days and the wounds were judged for cosmetic outcome. Four 1 x 3-cm strips of skin were excised from each wound; one strip for histologic analysis and three for load extension testing using a tensiometer. Specimens were loaded to wound failure while displacement (D) and energy absorption (EA) were recorded. The paired t-test was used for comparisons and reported as mean +/- SE. No significant difference between TG and suture was found in D (6.5 +/- 0.4 vs 5.2, 1.4 mm), EA (0.18 +/- 0.01 vs 0.17 +/- 0.03 kg x mm/cm2), or histologic features. The closure time was significantly less using TG (66 +/- 5 vs 401 +/- 17 sec; $p < 0.0001$). They found: 1) Sutures and TG in rat skin repair result in similar wound strengths (EA), amounts of stretch (D), and histologic feasures. 2) Wound closure is accomplished much more rapidly with TG (23).

Recently, Ritterband. et al determined the efficacy of a tissue adhesive (2-octyl cyanoacrylate) sealing clear corneal cataract wounds. Seven human donor globes were prepared for Miyake video microscopy. A 3.0 mm clear corneal incision was created. A transscleral cannula was inserted and connected to a bottle of saline. The bottle height was varied to alter intraocular pressure. Droplets of India ink were placed on the wound. Main outcome measure was any influx of India ink into the anterior chamber as viewed through the Miyake system with intraocular pressure (IOP) fluctuation or with manual pressure. If India ink was present in the eye, it was irrigated out, and the experiment was repeated with IOP fluctuation and manual pressure after the application of 2-octyl cyanoacrylate to the wound. One eye demonstrated the presence of India ink inside the eye on IOP reduction to <5 mm Hg. Three eyes demonstrated the presence of India ink inside the eye with manual pressure. Three eyes did not leak with manual pressure or IOP variation. All seven eyes without glue leaked with exaggerated manual pressure at the wound edge. Of the seven eyes with tissue adhesive, none demonstrated influx of India ink with IOP variation or manual wound manipulation. Their laboratory model demonstrates that 2-octyl cyanoacrylate prevents the influx of ocular surface fluid independent of IOP and manual wound manipulation. Further investigations in clinical models are necessary to determine the future use of this adhesive barrier substance (24).

Pervious reports on the use of OCA focused on the treatment of shallow wounds such as from superficial ulcers. In this study we have shown that OCA could be also used in deeply wound. Therefore, given the speed and efficacy of this new tissue adhesive, it should firmly establish itself in the treatment repertoire for closure of the skin. Future investigations with this product no doubt will expand its use.

Conclusion

We conclude that OCA (octyl-2-cyanoacrylate tissue glue) accelerates healing of full thickness wound of skin in mice.

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