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Can we use superglues for superficial lacerations?

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Abstract

Objectives: To compare the histopathological and cosmetic outcomes of ethyl-cyanoacrylate to n-butyl-2-cyanoacrylate in rats using an incision wound model.

Methods: Two longitudinal incisions were made on the dorsal region of the back of 18 Wistar rats after ketamine anesthesia. Rats were divided into three groups of six: the incisions were closed either using medical tissue adhesive or superglue or were left for secondary wound healing. In each group, three rats were randomly euthanized on the 7th day. The rest were euthanized on the 21st day of the procedure. Tissue samples taken on days 7 and 21 were Histopathologically evaluated blindly by a histologist. The cosmetic appearance was evaluated by a plastic surgeon blinded to the method of closure using a visual analog scale.

Results: Histopathological evaluation revealed impaired epithelialization, inflammation, fibrosis, and dehiscence on connective tissue, and foreign substance reactions were worse in the ethyl-2-cyanoacrylate group when compared with the other groups. A statistically significant difference was not found among groups regarding the cosmetic outcome.

Conclusions: Cyanoacrylate glues produced for commercial purposes should not be used for the repair of skin lacerations due to their worse histopathological results of epithelialization, inflammation, fibrosis, dehiscence on connective tissue, and foreign substance reaction.

Keywords: Lacerations, Wound closure techniques, Tissue adhesives, Cyanoacrylates, Wound healing.

Key Messages

- The first invented cyanoacrylate-based adhesives were used as tissue adhesives for many years. These commercial products are known as superglues, which are considerably cheaper than their medical-grade products.
- This study was designed to compare the histopathological and cosmetic outcomes of ethyl-cyanoacrylate (a commercial product used as super glue) to n-butyl-2-cyanoacrylate (produced for medical purposes) in 18 female Wistar rats using an incision wound model.
- Histopathological evaluation revealed impaired epithelialization, inflammation, fibrosis, dehiscence on connective tissue, and foreign substance reaction were worse in ethyl-2-cyanoacrylate group when compared with n-butyl-2-cyanoacrylate and secondary wound healing groups.
- Statistically significant differences were not found among groups regarding the cosmetic outcome.

Introduction

Traumatic injuries including lacerations are one of the most encountered problems in the Emergency Department (ED) and account for about 7% to 8% of all ED visits [1, 2]. Lacerations may be closed by one of four commonly available methods or devices: sutures, staples, adhesive tapes, or tissue adhesives. Each technique has some advantages and disadvantages over others [3, 4]. Cyanoacrylate-based tissue adhesives are approved to be used for laceration management. However, there are quite different forms of cyanoacrylate-based adhesives that are marketed as superglues for household and industrial use and as much more expensive forms for medical use. Cyanoacrylate adhesives were invented by Drs. Coover and Joyner in 1942 and globally known as superglues [5]. Methyl-2-cyanoacrylate was used to bond skin and control bleeding in open wounds in the 1950s and 1960s. Disposable sprays were extensively used over wounds to stop bleeding in the Vietnam War. Meanwhile, the Food and Drug Administration (FDA) changed standards and kept requesting additional data since methyl-2-cyanoacrylate provoked acute and chronic tissue reactions [6].

Currently, available medical-grade products contain butyl, isobutyl, or octyl esters. N-butyl-cyanoacrylate has been used in Europe since the 1970s for a variety of surgical applications. It was not until 1998 that n-2-octyl cyanoacrylate was approved by the FDA for use in the United States. However, there is still limited and conflicting data about the use of superglues for wound closure [6-8]. They are considerably cheaper than their medical-grade products. And the reason why we cannot use them for superficial lacerations should be clarified. This study aims to compare the histopathological and cosmetic outcomes of ethyl-2-cyanoacrylate (a commercial product used as super glue) to n-butyl-2-cyanoacrylate (produced for medical purposes) used for incisional wound models in rats.

Materials and Methods

This experimental randomized controlled study was done in the Care and Production Unit of Research Animals at the Akdeniz University School of Medicine. The experimental protocol complied with the Helsinki Convention and Akdeniz University Local Ethics Committee on Animal Research approved the study. Eighteen female Wistar rats weighed between 220 and 250 grams were anesthetized using 10 milligrams/kg Ketamine and 50 milligrams/kg Xylazine. Two longitudinal incisions were made 1 cm from the midline on the dorsal region of the back of each rat by using a #20 surgical scalpel blade. The depth of the incisions was about 2 mm, including the skin and the subcutaneous tissue. Incisions were parallel to each other and were made to double the number of wounds and tissue samples.

Bleeding was controlled by applying direct pressure for approximately 10 to 15 minutes. Rats were divided into three groups of six in each: the incisions were closed either using medical tissue adhesive (n-butyl-2-cyanoacrylate, Liquiband®, Advanced Medical Solutions Limited, United Kingdom) or superglue (ethyl-2-cyanoacrylate, Pattex®, Henkel AG & Co. KGaA, Germany) [9] or were left for secondary wound healing only covering with gauze. Wound edges were opposed before the adhesives were applied over the laceration and drying time after application of adhesives was measured with a stopwatch. Rats were kept in an air-conditioned room and fed regularly. Acetaminophen liquid was given via drinking water for 2 days after the procedure; however, the antibiotic was not administered.

In each group, three rats were randomly euthanized on the 7th postoperative day and the others were euthanized on the 21st postoperative day of the procedure after they were anesthetized with ether. Digital photographs were taken in a standardized manner with a Nikon® D5000 digital camera for macroscopic evaluation. Cosmetic appearance was evaluated by a plastic surgeon blinded to the method of closure using a visual analog scale (VAS). The VAS cosmesis scale was a 100-mm line with a “best scar” at the left end (0 mm) and a “worst scar” at the right end (100 mm).

Tissue samples taken on the 7th and 21st postoperative days were put in vials filled with 10% formaldehyde and stained with hematoxylin-eosin. Stained specimens were Histopathologically evaluated blindly by a histologist. The development of epithelialization, inflammation, fibrosis, dehiscence on connective tissue, foreign substance reaction, and necrosis were noted. Data were analyzed using SPSS version 13.0 (SPSS Inc., Chicago, IL). Continuous variables were described as mean and standard deviation and categorical variables as percentages. The Shapiro-Wilk Test was performed to test for the normality of data. One-way ANOVA was used to compare the normally distributed two groups. Non-normally distributed three or more groups were compared with the Kruskal-Wallis Test. The chi-square test was used to compare categorical variables. Post hoc analysis was done with Tukey HSD and Bonferroni correction. The Wilcoxon signed-rank test was used to compare two groups with repeated measures. Hypotheses were accepted as a two-tailed and alpha critical value was set at 0.05.

Results

Sixteen rats were anesthetized one after another, incisions were made, and wound care was performed as

described in the methods section. None of the rats died during or just after the procedure and during the follow-up period. The mean drying times were calculated as 66±12 seconds in the n-butyl-2-cyanoacrylate group and 390±85 seconds in the ethyl-2-cyanoacrylate group (p=0.000). On the 7th day, granuloma was seen around the laceration site of one of the ethyl-2-cyanoacrylate group rats.

A plastic surgeon blindly reviewed photos of the wounds taken on the 7th (Figure 1) and 21st days. No statistically significant difference was found among groups according to the cosmetic outcome on the 7th day (p=0237). A statistically significant difference was found among the 3 groups on the 21st day (p=0.041), however when Bonferroni correction was applied for this group, no significant difference was found (Table 1). When the cosmetic outcome was evaluated according to the days of healing, a statistically significant difference was found in each group (Table 1).

Histopathological evaluation revealed impaired epithelialization. Inflammation, fibrosis, dehiscence on connective tissue, and foreign substance reaction were worse in ethyl-2-cyanoacrylate closings compared to n-butyl-2-cyanoacrylate and secondary wound healing (Table 2 and Figures 2,3). Five of 6 rats (83%) in the ethyl-2-cyanoacrylate group demonstrated moderate to severe fibrosis on the 21st day of healing, whereas 5 of 6 rats in the n-butyl-2-cyanoacrylate group did not have or demonstrated mild fibrosis. Foreign body reaction was determined in 2 rats in the ethyl-2-cyanoacrylate group, however none in n-butyl-2-cyanoacrylate or the control groups. Eosinophil and basophil cells were seen in the ethyl-2-cyanoacrylate group on the 21st day. (Figures 3-7) Necrosis was not present in any of the groups.

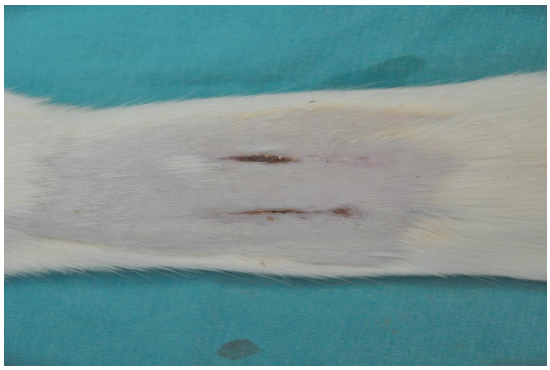

Figure 1: Incision closures with n-butyl-2-cyanoacrylate on day 7.

Table 1: Cosmetic outcomes of wound healing on the visual analog scale on the 7th and 21st postoperative days.

Groups	*Mean of VAS (mm)*		*p-value (Difference of VAS scores between the 21st and 7th days for each method)*
	7th day	*21st day*	
N-butyl-2-cyanoacrylate	58.3±20.7	12.5±6.1	0.027
Ethyl 2-cyanoacrylate	75.0±18.4	17.5±8.2	0.026
Control	60.0±13.8	25.8±9.7	0.027
p-value (Difference of VAS scores among groups on the 7th and 21st days)	0.237	0.041	

Table 2: Histopathological results.

		7th day			*21st day*	
	BCA	**ECA**	**Control**	**BCA**	**ECA**	**Control**
Epithelialization *Straight*	5	3	3	5	5	6
Discrete	1	3	3	1	1	0
Inflammation *None*	6	5	4	6	5	6
Mild	0	1	2	0	1	0
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Fibrosis *None*	6	4	4	4	1	5
Mild	0	2	2	1	0	1
Moderate	0	0	0	0	3	0
Severe	0	0	0	1	2	0
Dehiscence on connective tissue *None*	3	1	4	4	1	5
Mild	2	1	2	1	1	1
Moderate	1	3	0	1	2	0
Severe	0	1	0	0	2	0
Foreign substance reaction *None*	6	5	6	6	4	6
Present	0	1	0	0	2	0

Abbreviations: BCA: n-butyl-2-cyanoacrylate; ECA: ethyl-2-cyanoacrylate©

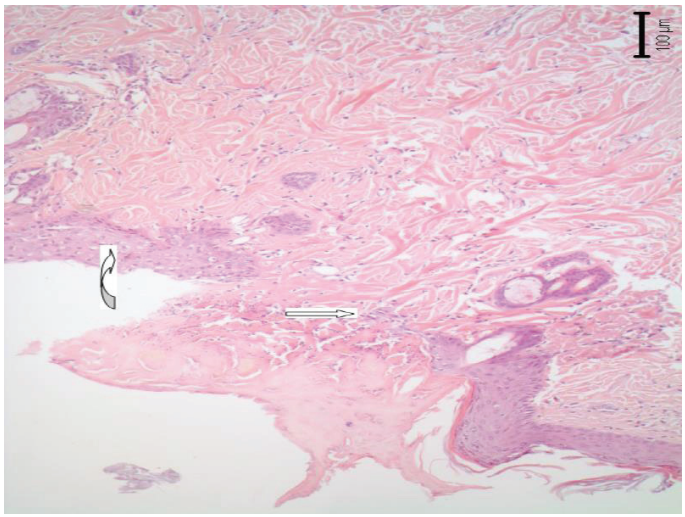

Figure 2: Tissue sample of the control group on the 7th day. Epithelialization has not been completed yet (curved thick double arrow). Collagen fibers are seen with leukocyte infiltration (downwards thick arrow) and the development of scar tissue. (Magnification: 10X).

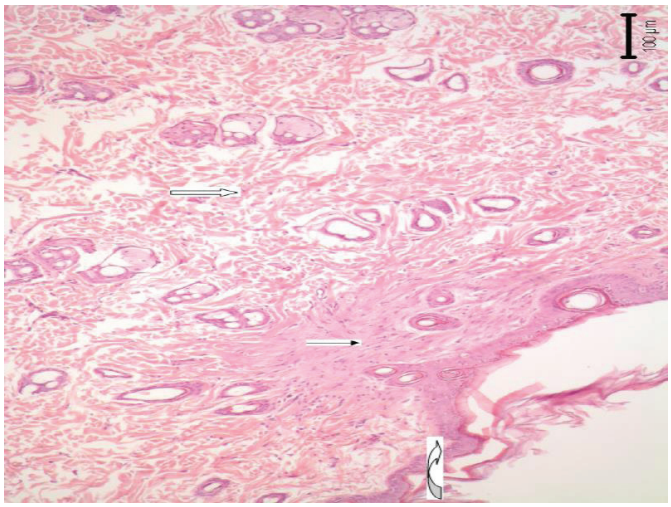

Figure 3: Tissue sample of ethyl-2-cyanoacrylate group on the 7th day. Dehiscence on connective tissue (downwards thick arrow) and fibrosis (downwards arrow) is seen. Epithelialization (curved thick double arrow) develops appropriately. (Magnification: 10X).

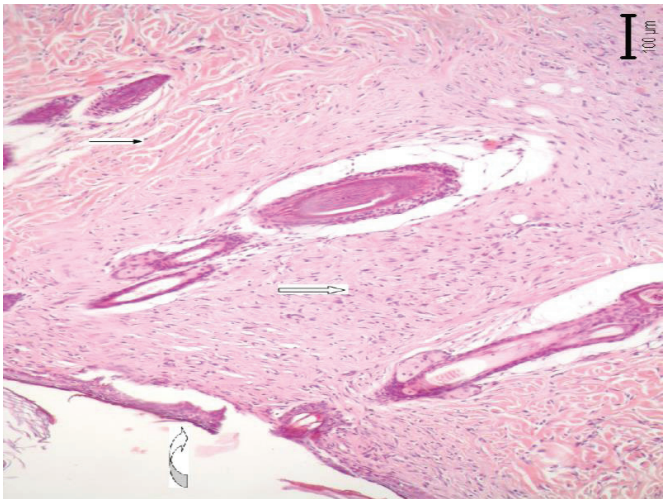

Figure 6: Tissue sample of ethyl-2-cyanoacrylate group on the 21st day. Epithelialization is poor (curved thick double arrow) and fibrosis is seen diffusely (downwards thick arrow). The collagen structure (downwards arrow) is dense and different from normal wound healing. (Magnification: 10X).

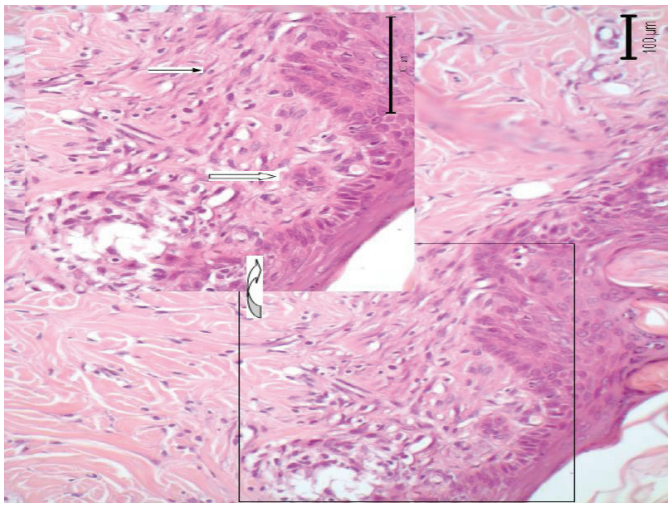

Figure 4:Tissue sample of ethyl-2-cyanoacrylate group on the 7th day. Foreign substance reaction, giant cells under the epithelium (downwards thick arrow) and fibrosis (downwards arrow) are seen. (Magnifications: 10X and 40X).

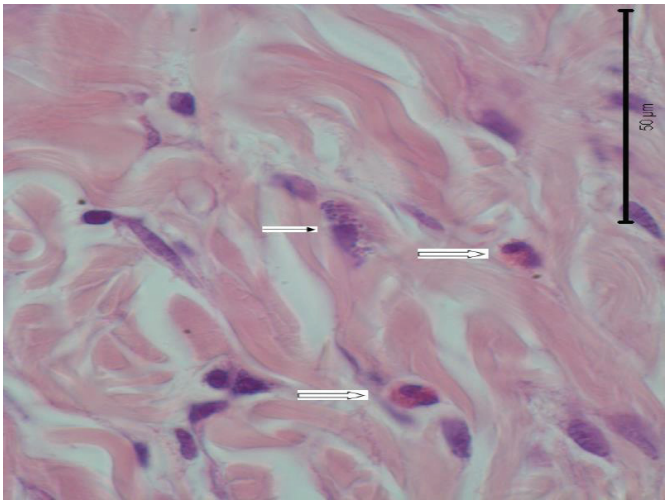

Figure 7: Tissue sample of ethyl-2-cyanoacrylate group on the 21st day. Infiltration of eosinophils (downwards thick arrows) and a basophil (downwards arrow) is seen. (Magnification: 100x).

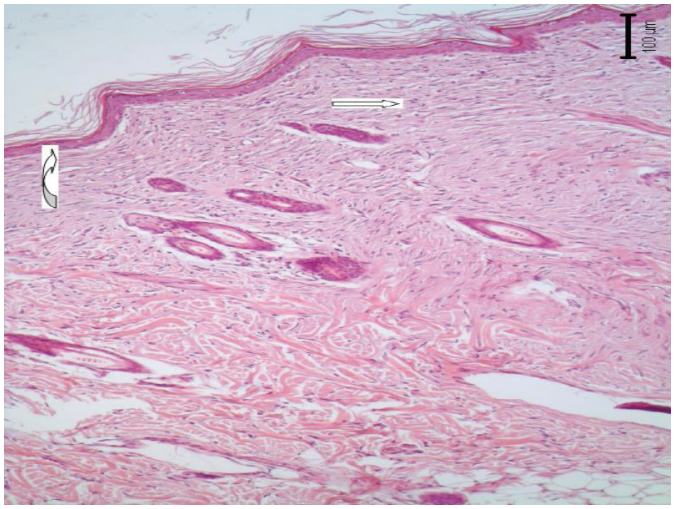

Figure 5: Tissue sample of ethyl-2-cyanoacrylate group on the 7th day. Foreign substance reaction, giant cells under the epithelium (downwards thick arrow) and fibrosis (downwards arrow) are seen. (Magnifications: 10X and 40X).

Discussion

The use of cyanoacrylate adhesives for wound closure has evolved significantly, with recent formulations showing considerable improvements over earlier versions. This study investigates the histopathological outcomes associated with ethyl-2-cyanoacrylate (commonly known as superglue) compared to n-butyl-2-cyanoacrylate (a medical-grade adhesive), shedding light on their respective impacts on wound healing.

Histopathological Findings

Our results demonstrate that ethyl-2-cyanoacrylate is linked with more severe histopathological effects than n-butyl-2-cyanoacrylate. Specifically, wounds closed with ethyl-2-cyanoacrylate exhibited impaired epithelialization,

increased inflammation, more extensive fibrosis, and a greater frequency of foreign body reactions. These findings are consistent with literature indicating that ethyl-2-cyanoacrylate often causes significant tissue irritation due to its rapid polymerization and byproducts [10, 11].

Chemical Composition and Tissue Reaction

Ethyl-2-cyanoacrylate, a shorter-chain cyanoacrylate, polymerizes more exothermically and quickly upon exposure to moisture, leading to excessive heat and degradation products that exacerbate inflammatory responses [12]. This rapid polymerization results in a rigid bond that can cause additional local irritation. Conversely, n-butyl-2-cyanoacrylate, with its longer alkyl chain, polymerizes more slowly and with less heat generation, which reduces inflammatory responses and improves biocompatibility [13]. These properties contribute to its favorable performance in clinical settings.

Clinical Implications and Comparisons

The transition from methyl-2-cyanoacrylate to n-butyl-2-cyanoacrylate and octyl-2-cyanoacrylate in medical applications reflects the latter's improved safety profile. Methyl-2-cyanoacrylate was initially used but phased out due to severe tissue reactions [14]. Modern medical-grade adhesives, including n-butyl-2-cyanoacrylate, have been shown to offer better outcomes in terms of wound dehiscence and cosmetic results compared to traditional sutures and non-medical adhesives [15, 16].

Cosmetic Outcomes

Although our study did not find statistically significant differences in cosmetic outcomes between adhesives and secondary healing, trends suggest that n-butyl-2-cyanoacrylate generally provides better cosmetic results. This is supported by research indicating that medical-grade adhesives tend to produce superior cosmetic outcomes due to their reduced inflammatory potential and optimized formulation [17, 18].

Drying Time

The observed difference in drying times—66 seconds for n-butyl-2-cyanoacrylate versus 390 seconds for ethyl-2-cyanoacrylate—highlights the practical advantages of medical-grade adhesives. The faster drying time of n-butyl-2-cyanoacrylate facilitates quicker wound closure, which is crucial in emergency settings [20]. In contrast, the prolonged drying time of ethyl-2-cyanoacrylate may complicate its clinical application and effectiveness.

Future Research Directions

Future research should focus on:

- Mechanisms of Action: Exploring the molecular mechanisms underlying the tissue interactions of different cyanoacrylate adhesives to better understand their varying impacts on inflammation and healing [21].
- Comparative Studies: Conduct extensive studies in larger animal models and human trials to validate these findings and evaluate the performance of various cyanoacrylate formulations in diverse clinical scenarios [22].
- Alternative Formulations: Investigating new cyanoacrylate formulations with improved biocompatibility and reduced inflammatory potential could provide enhanced options for wound closure [23-25].

Conclusion

In conclusion, while ethyl-2-cyanoacrylate is a cost-effective adhesive, its adverse histopathological effects make it unsuitable for wound closure. Medical-grade adhesives like n-butyl-2-cyanoacrylate offer a safer and more effective alternative, supporting better wound healing and cosmetic outcomes. This study underscores the importance of choosing appropriate medical adhesives to ensure optimal patient safety and wound management.

Acknowledgment

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