

**Original Article**

# Histological and Immunohistochemical Study on the Effect of Cyanoacrylate Topical Adhesive on Healing of Skin Wounds Versus Vicryl Suture Among Rabbits

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## Abstract:

**Aim:**The objective of study was to evaluate the effect of cyanoacrylate tissue adhesive on healing of skin wounds versus vicryl suture among rabbits through histological examination and immunohistochemical detection of Transforming growth factor beta 1 (TGF- $\beta$ 1) and Tumor necrosis factor alpha (TNF- $\alpha$ ).

**Materials & Methods:** This study was carried out on 10 rabbits which subjected to the same surgical procedures as skin incisions were performed then the rabbits were divided into two equal groups of five animals each, Group I (control group); Whose skin wounds were closed with 3-0 vicryl suture and Group II (study group); Cyanoacrylate Glue were applied only on the site of wound with observation periods of two weeks. At the end of experiment, the skin tissues were removed and processed for the histological examination and immunohistochemical analysis.

**Results:**The histological results showed that skin specimens of control rabbit stained with hematoxylin and eosin stain two weeks after surgery revealed formation of thin epithelial layer with absence of epithelial ridges while the skin of the experimental site revealed increased epithelial thickness. Skin wounds of control site stained with Masson's trichrome stain revealed mild positive staining reaction while skin wounds of the experimental site showed strongly positive staining reaction. The immunohistochemical localization of transforming growth factor beta (TGF-  $\beta$ 1) revealed that examination of specimens of control site showed weak positive staining reaction while skin wounds of the experimental site showed strongly positive staining reaction. Immunohistochemical localization of tumor necrosis factor alpha (TNF- $\alpha$ ) showed that examination of skin specimens of control site showed weak to moderate positive staining reaction while skin wounds of the experimental site showed weak positive staining reaction.

**Conclusion:** The cyanoacrylate adhesive accelerates the healing process of skin wounds in rabbits.

**Key words:** Skin Wounds, Cyanoacrylate adhesive, Vicryl suture.

## Introduction:

The biological mechanism of skin wound healing has been significant to mammals throughout evolution<sup>1</sup>. Skin wound therapies could be classified into “Conventional” or “Regenerative”. Conventional therapy leads to the formation of scars irrespective of aesthetic and possible functional alterations<sup>2</sup>. Regenerative wound therapy is a fresh and rapidly progressing area of biomedical research with the goal to regenerate damaged cells and skin tissue without leaving scars<sup>3</sup>.

In any event, regeneration strategies should be considered additional to essential conventional treatments, such as debridement<sup>4</sup>. Sutures, staples, clips, skin closure strips and topical adhesives can all be used to simulate the wound healing. Advantages of tissue adhesives over conventional sutures include easy to use, excellent bacteriostatic activity, decreased repair time and good cosmetic outcome<sup>5</sup>.

In general surgery, cyanoacrylate adhesives have long been used as an alternative to sutures for the intention of closing surgical wounds. They have been used in oral surgery for a variety of things, such as periodontal treatment, sinus membrane regeneration, anchoring broken bone fragments during fracture fixation and sealing peripheral nerve anastomoses<sup>6</sup>. They have also been suggested for wound closure by primary intention and, more recently, for coating bleeding surfaces healed by secondary intention<sup>7</sup>.

Cyanoacrylate tissue adhesives are of great interest in surgery because of their excellent hemostasis, rapid adherence to tissues and bacteriostatic potential. They can also be administered more quickly than conventional sutures<sup>8</sup>. The use of cyanoacrylate is currently only permitted in certain people with diseases that could change the normal course of clotting,

healing, skin allergies, wounds with inadequate hemostasis, and wounds with probable infection risk in mucosal membranes<sup>9</sup>.

Adhesives manufactured of N-butyl cyanoacrylate have bacteriostatic and hemostatic features<sup>10</sup>, lengthy half-life (initial disintegration after the third week) and also optimal tissue compatibility when used to close surgical wounds instead of ordinary suture materials<sup>11</sup>.

Numerous recent studies have discovered that using cyanoacrylate as a wound dressing for the treatment of open wounds as well as wound closure does not cause tissue toxicity<sup>12,13</sup>.

Prior to applying the N-butyl cyanoacrylate, the wound must be well cleaned and dried. Any wetness or bleeding sites must be avoided as they may hasten the polymerization process and raise the possibility of dehiscence. The amount to be used will depend on how far the wound extends<sup>14</sup>.

It has demonstrated successful esthetic healing of lacerations with few consequences. The assumption made the null hypothesis stated that closing incisions in the maxillofacial region with tissue adhesive would speed up wound healing while preserving or improving cosmesis and preventing morbidity<sup>15</sup>.

Finally, the possibility of surgical wound care requires the using local anesthesia or even total anesthesia to young toddlers and mentally handicapped people patients. Tissue glue with exceptional tensile strength and ease of usage has been made available to surgeons thanks to recent advancements in synthetic polymer technology<sup>16</sup>. Such adhesives guarantee quicker application, increased patient comfort, and possibly accelerated healing<sup>17</sup>. The cyanoacrylates have several of these qualities<sup>18</sup>.

So the present study will evaluate if cyanoacrylate tissue adhesive can be effective on healing of skin wounds histologically and immunohistochemically.

Aim of the study:

This investigation compares the effects of vicryl suture and cyanoacrylate tissue glue on rabbits' skin wound healing through histological (hematoxylin and eosin, Masson's trichrome stain) examination and immunohistochemical detection of Transforming growth factor beta 1 (TGF- $\beta$ 1) and Tumor necrosis factor alpha (TNF- $\alpha$ ).

I- Material:

Material that was used in the present study is Histoacryl (Butyl-2-cyanoacrylate), manufactured by B. Braun, Melsungen AG, Germany.

II- Methods:

II.1- Sample size calculation

Sample size calculation was performed using G\*Power version 3.1.9.2, Faul *et al*, (2007)<sup>19</sup>.

The effect size  $d$  was 2.30 using  $\alpha$  level of 0.05 and Beta ( $\beta$ ) level of 0.05, i.e., power = 95%; the estimated sample size ( $n$ ) should be 10 samples (rabbit) for this study and were divided equally in two main groups (5 rabbits each).

II.2 Study setting and sample selection:

The present study was commenced after the approval of the Research Ethics Committee of the faculty of Dentistry, Suez Canal University established according to "WHO-2011" (no. 550/2022).

This study was carried out on 10 healthy adult male rabbits (average weight 1.5 kg).

Rabbits were housed separately in clean metal cages under standard condition, controlled lightening and environmental temperature (25°C) receiving a standard laboratory diet and water.

II.3-Samples grouping and study procedures:

The animals were anesthetized with Ketamine (40mg /kg body weight) intramuscularly.

All animals were subjected to the same surgical procedures as skin incisions were performed.

The rabbits were divided into two equal groups of five animals each, with observation periods of two weeks:

Group I (control group):- Whose skin wounds were closed with 3-0 vicryl suture on the wound margins, then the wound were left to heal spontaneously without any materials added.

Group II (study group):- Cyanoacrylate Glue were applied only on the site of wound.

At the end of experiment, all rabbits were euthanized. The skin tissues were removed and fixed in 10% buffered formaldehyde, processed histologically, embedded in paraffin and subjected to 4-mm cuts for staining by haematoxylin and eosin (H&E) and Masson's trichrome for collagen demonstration.

II.4-Evaluation methods:

I- Immunohistochemical analysis:

The slides were dewaxed and submitted to antigenic recovery with 0.1 M citrate solution Ph 6.0. Endogenous peroxidase activity was blocked for 30 min with 0.3% hydrogen peroxide followed by 1% protein blocking for 30 min. The slides were incubated overnight with the following antibodies: anti-transforming growth factor beta 1 (TGF- $\beta$ 1) and anti-tumor necrosis factor alpha (TNF- $\alpha$ ).

III- Statistical analysis:

Statistical analysis were performed using the computer program SPSS software for windows version 26.0 (statistical package for social

science, Armonk NY: IBM corp) at significant level 0.05 ( $p$ - value  $\leq 0.05$ ) Descriptive statics were calculated in the form Mean  $\pm$  Standard deviation. Independent samples T-test were used

#### IV- Ethics consideration:

The present research was conducted after the approval of the Research Ethics Committee (REC) of the Faculty of Dentistry, Suez Canal University established according to " WHO-2011" (no. 550/2022).

#### Results:

##### Haematoxylin and eosin (H&E):

Two weeks after surgery the skin of control rabbit treated with vicryl suture showed formation of thin epithelial layer with absence of epithelial ridges associated with degeneration of collagen fibers (Fig 1 A) while the skin of the experimental

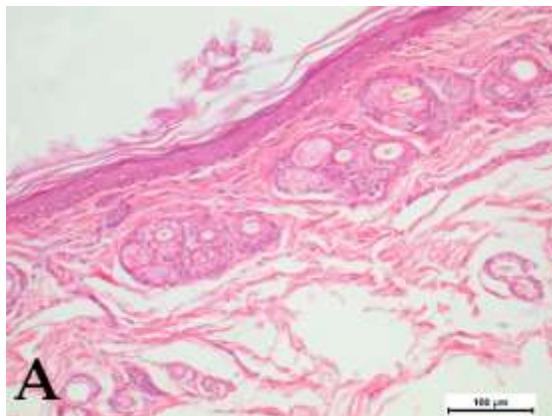
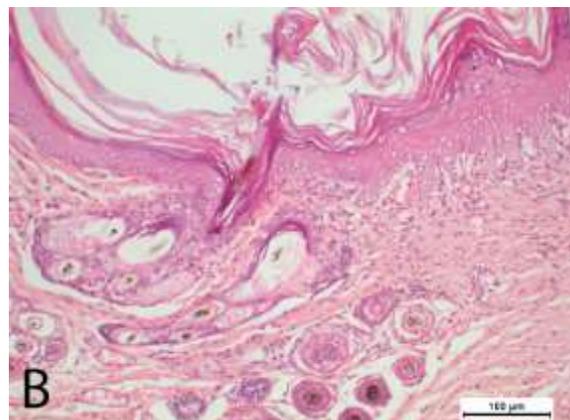


Fig 1: (A) Skin wound of control site showed formation of thin epithelial layer with absence of epithelial ridges associated with degeneration of collagen fibers (B) the skin of the experimental site revealed a progressive epithelialization and collagenization.

to compare between the two groups for each variable under study.  $P$  value  $\leq 0.05$  is considered be statistically significant

It were conducted on ten rabbits. Ethical considerations involving experimental animals were undertaken by the researcher and a pledge form for animal care were submitted to (REC) before commencing the study.

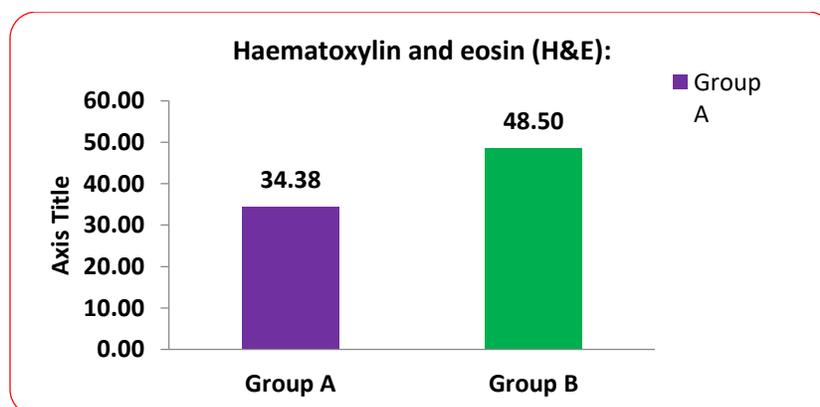
site which covered with a layer of cyano-acrylate adhesive revealed increased epithelial thickness with formation of epithelial ridges associated with increased keratinization in surface of wound, increased thickness of epidermis, increased activation of fibroblasts and thickness of collagen fiber (Fig 1 B).



Statistical analysis using independent sample T test showed significant difference between the two groups ( $P < 0.001^{**}$ ). The mean values for epithelial layer thickness in group B was higher ( $48.50 \pm 5.29$ ) than group A ( $34.38 \pm 4.73$ ) (Table 1)

Groups	Mean	SD	Indep. T-test	P value
Group A	34.38	4.73	5.45	<0.001**
Group B	48.50	5.29		

\*\*; means significant at P<0.01



#### Masson's trichrome stain:

Skin wounds of control site showed mild to moderate positive staining reaction of collagen fibers (Fig 2 A) while skin wounds of the

experimental site which covered with a layer of cyano-acrylate showed strongly positive staining reaction of collagen fibers for Masson's trichrome stain (Fig 2 B).

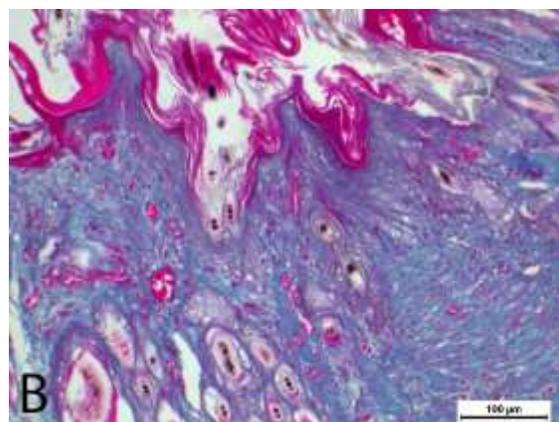
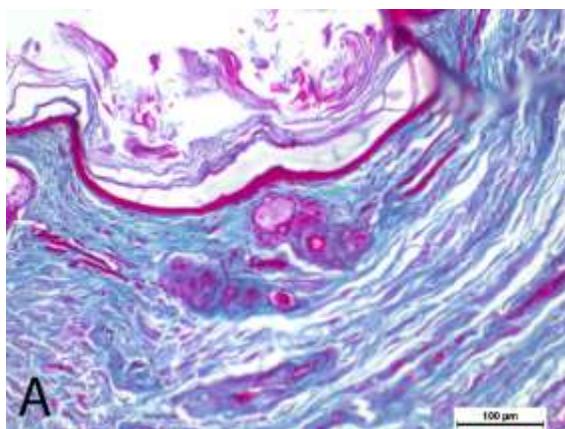


Fig 2: (A) Skin wound of control site showing mild to moderate positive staining reaction of collagen fibers (B) skin wounds of the experimental site showing strongly positive

staining reaction of collagen fibers for Masson's trichrome stain.

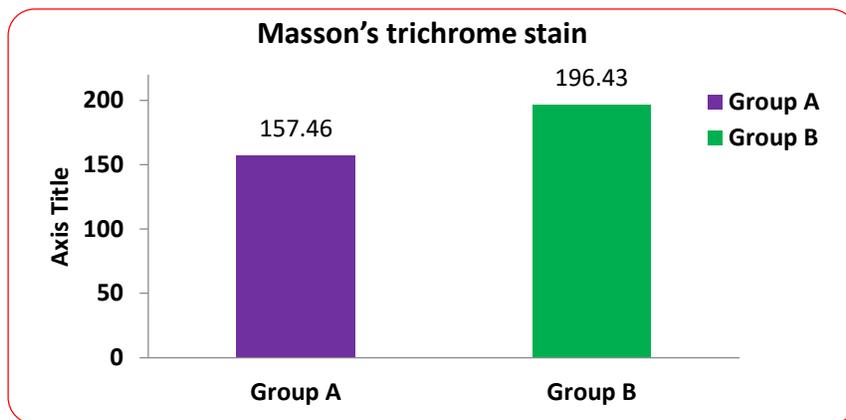
Statistical analysis using independent samples T test showed significant difference between the two groups ( $P < 0.001^{**}$ ). The mean values for staining reaction of collagen fibers for Masson's

trichrome stain in group B was higher ( $196.43 \pm 9.96$ ) than group A ( $157.46 \pm 7.83$ ) (Table 2).

Table 2,

Groups	Mean	SD	Indep. T-test	P value
Group A	157.46	7.83	10.721	$< 0.001^{**}$
Group B	196.43	9.69		

**\*\***; means significant at  $P < 0.01$



Immunohistochemical localization of transforming growth factor beta (TGF-  $\beta$ 1):

Examination of skin specimens of control site showed weak positive staining

reaction of cells and collagen fibers (Fig 3 A) while skin wounds of the experimental site was covered with a layer of cyano-acrylate showed strongly positive staining reaction of cells and collagen fibers (Fig 3 B).

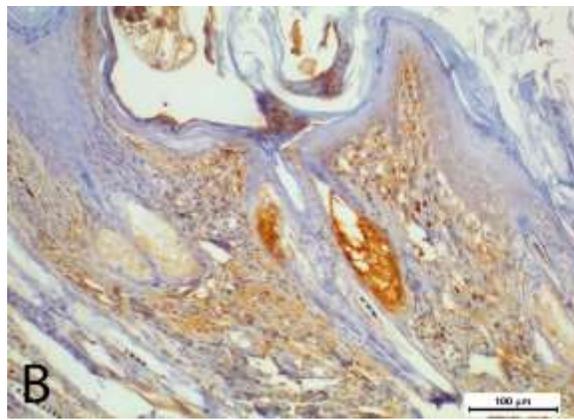
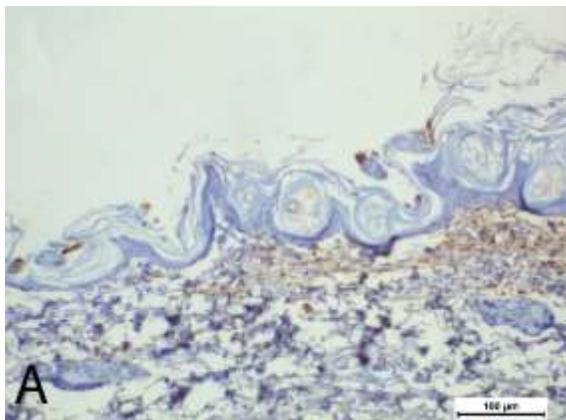


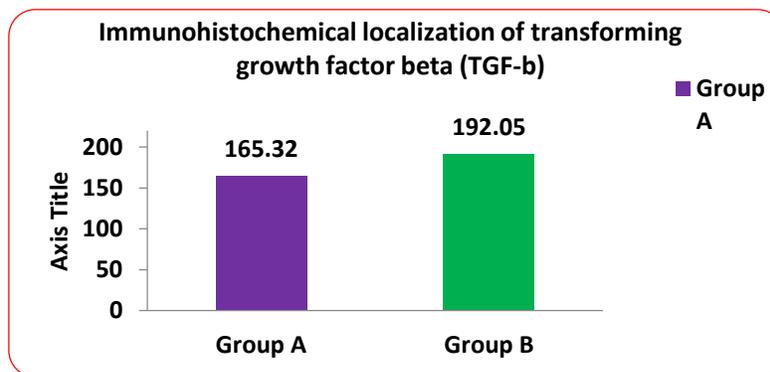
Fig 3: (A) Skin specimens of control site showing weak positive staining reaction of cells and collagen fibers (B) skin specimens of the experimental site showing strongly positive staining reaction of cells and collagen fibers.

Statistical analysis using independent samples T test showed significant difference between the two groups ( $P < 0.001^{**}$ ). The mean values for immunostaining reaction of skin specimens for transforming growth factor beta 1 (TGF- $\beta$ 1) in group B was higher ( $192.05 \pm 8.34$ ) than group A ( $165.32 \pm 7.16$ ) (Table 3).

Table 3,

Groups	Mean	SD	Indep. T-test	P value
Group A	165.32	7.16	8.447	<0.001**
Group B	192.05	8.34		

\*\*; means significant at  $P < 0.01$



Immunohistochemical localization of tumor necrosis factor alpha (TNF- $\alpha$ ):

Examination of skin specimens of control site showed weak to moderate positive staining

reaction of cells and collagen fibers (Fig 4 A) while skin wounds of the experimental site was covered with a layer of cyano-acrylate showed weak positive staining reaction of cells and collagen fibers (Fig 4 B).

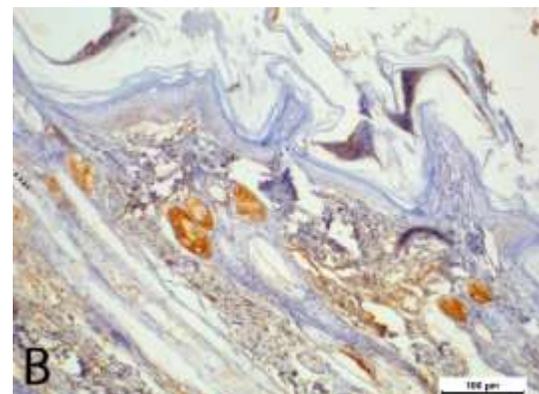
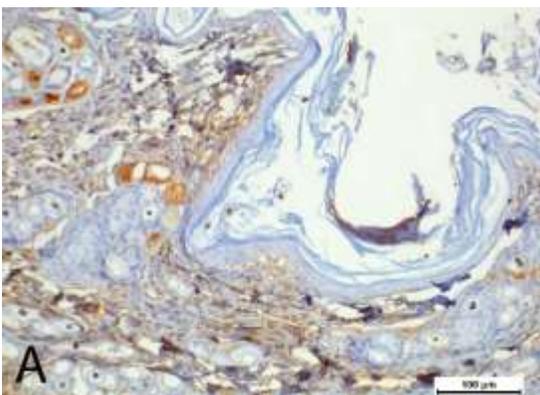


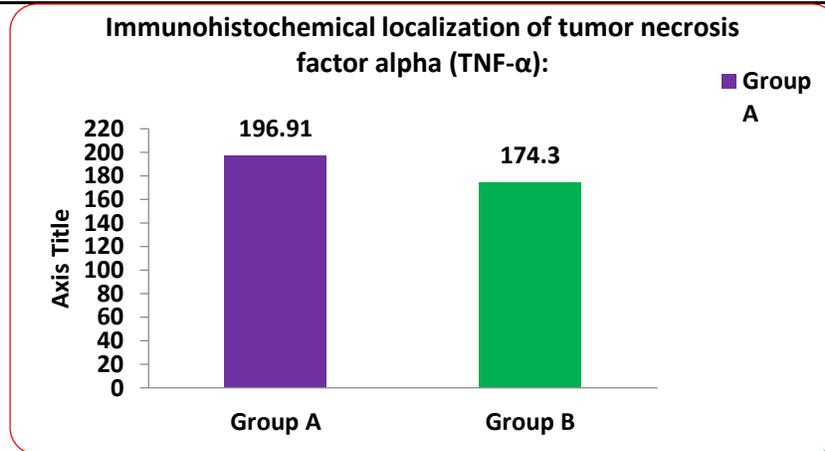
Fig 4: (A) Skin specimens of control site showing weak to moderate positive staining reaction of cells and collagen fibers (B) skin specimens of the experimental site showing weak positive staining reaction of cells and collagen fibers.

Statistical analysis using independent samples T test showed significant difference between the two groups ( $P < 0.001^{**}$ ). The mean values for immunostaining reaction of skin specimens for Tumor necrosis factor alpha (TNF- $\alpha$ ) in group A was higher ( $196.91 \pm 8.70$ ) than group B ( $174.3 \pm 6.53$ ) (Table 4).

Table 4,

Groups	Mean	SD	Indep. T-test	P value
Group A	196.91	8.70	8.46	<0.001**
Group B	174.3	6.53		

\*\*; means significant at  $P < 0.01$



**Discussion:**

The present study confirms experiment in skin wounds which shows the effects of vicryl suture and cyanoacrylate tissue glue on rabbits' skin wound healing.

One of the clinical benefits of cyanoacrylates is the potential for polymerization when cyanoacrylates come into contact with water and/or blood due to their superior tissue bonding strength<sup>20</sup>.

Although butyl-2-cyanoacrylate works well to close superficial wounds under low stress, it has a number of drawbacks. When used in extensive incisions in the skin, the glue becomes brittle after polymerizing and is vulnerable to fracturing<sup>21</sup>.

In the current study, skin specimens of control rabbit two weeks after surgery revealed formation of thin epithelial layer with absence of epithelial ridges associated with degeneration of collagen fibers while a layer of cyano-acrylate adhesive was applied to the experimental site's skin revealed increased epithelial thickness with formation of epithelial ridges, increased activation of fibroblasts, keratinization of the wound's surface, epidermal thickness, and collagen fiber thickness. These results were confirmed with the use of Masson's trichrome stain which showed that skin wounds of control site revealed mild positive staining reaction of collagen fibers while a layer of cyano-acrylate

adhesive was applied to the experimental site's skin showed strongly positive staining reaction of collagen fibers for Masson's trichrome stain.

According to recent studies, using cyanoacrylate tissue adhesive to close traumatic lacerations and incisional surgical wounds produces cosmetic results that are equivalent to those achieved with traditional sutures<sup>22</sup>.

The use of cyanoacrylate has been widespread and has produced good cosmetic results for different plastic surgery operations (eg, upper lid blepharoplasty, facial skin closure, scalp wound closure).

The histological results were confirmed by the immunohistochemical localization of transforming growth factor beta (TGF-  $\beta$ 1) study which revealed that examination of skin specimens of control site showed weak positive staining reaction of cells and collagen fibers while skin wounds of the experimental site was covered with a layer of cyano-acrylate showed strongly positive staining reaction of cells and collagen fibers.

The increased expression of TGF-  $\beta$ 1 is necessary to induce collagen synthesis.

Immunohistochemical localization of tumor necrosis factor alpha (TNF- $\alpha$ ) showed that examination of skin specimens of control site showed weak to moderate positive staining reaction of cells and collagen fibers while a layer of cyano-acrylate adhesive was applied to the experimental site's skin showed weak positive staining reaction of cells and collagen fibers.

The cyanoacrylates offer antibacterial capabilities against gram-positive organisms, serve as waterproof occlusive dressings and may reduce infections. When compared to suture closure, they have been shown to reduced incidence of histologic and clinical infection in contaminated wounds. Inappropriate insertion of

adhesives into wounds might cause a foreign-body reaction and raise infection rates<sup>23</sup>.

Additionally, Gram-positive, Gram-negative motile and nonmotile organisms are unable to penetrate the cyanoacrylate film in vitro<sup>24</sup>.

Although there is no data to conclusively show that cyanoacrylate causes human cancer, it can be harmful to the nervous and respiratory systems and cause contact dermatitis and urticaria. Dental professionals and other workers should take precautions to prevent direct contact with cyanoacrylate and minimize environmental exposure due to these side effects<sup>25</sup>.

In contrast to our results with suture specimens, we did not find any presence of severe inflammatory responses or abscesses in the biopsies of glue-treated wounds. This might indicate that the adhesive is more biocompatible. According to certain reports, cyanoacrylates have a bactericidal effect<sup>26</sup>. On the other hand, it has been reported that due to some suturing materials' susceptibility for bacteria, sutures raise the risk of infection.

However, AJOG (2017) concluded that the technique for skin closure should be determined by the surgeon's judgment and the availability of materials because wound closure with both approaches is comparable in terms of both safety and final cosmetic outcome<sup>27</sup>.

Because of its ease of use, speed of administration, reduced trauma and comfort for patients, N-butyl cyanoacrylate is regarded as a great option for closing skin wounds<sup>28</sup>.

#### **Conflict of Interest:**

The authors declare no conflict of interest.

#### **Funding:**

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sector

**Ethics:**

This study protocol was approved by the ethical committee of the faculty of dentistry- Suez Canal University on: 1<sup>st</sup> of November 2022, approval number: (no. 550/2022).

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