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Histopathological effects of ethyl 2-cyanoacrylate tissue adhesive following surgical application: an experimental study

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Abstract

Objective: To investigate experimentally the possible histopathological effects of ethyl 2-cyanoacrylate glue when used as a tissue adhesive in cardiovascular and thoracic surgery. **Methods**: Sprague–Dawley rats were used for this study. For histopathological investigation, a study group of 144 rats in which intentionally produced lesions in myocardium ($n = 36$), ascending aorta ($n = 36$), lung ($n = 36$) and abdominal aorta ($n = 36$) were closed by using ethyl 2-cyanoacrylate was compared with the control group ($n = 144$) in which the same lesions were closed by using sutures. On each of days 1, 7, 15, 30, 45 and 60, six rats from the study group and six rats from the control group were sacrificed and analyzed for each relevant organ in terms of bonding of ethyl 2-cyanoacrylate polymers to tissue, foreign body reaction, inflammatory reactions, and necrosis. Endothelial cell damage, intimal hyperplasia, and thrombus formation were also evaluated in arteriotomy sections. **Results**: In histopathological analysis of vascular, myocardial and pulmonary tissue sections, there was no significant histopathological difference between conventionally sutured tissues and ethyl 2-cyanoacrylate-applied tissues. **Conclusions**: As no significant difference between conventional suture and ethyl 2-cyanoacrylate application was detected in terms of histopathological reactions, ethyl 2-cyanoacrylate may be considered as an alternative or adjunct to conventional techniques in controlling hemorrhage that cannot be controlled by conventional methods, in tissue repair and in the control of pulmonary air leakage, and may be used in vascular, myocardial and pulmonary surgery.

Keywords: Cardiovascular surgery; Thoracic surgery; Ethyl 2-cyanoacrylate; Tissue adhesive; Histopathological effects

1. Introduction

For cardiovascular surgery, uncontrollable hemorrhage, impaired tissue integrity, sternal dehiscence and for pulmonary surgery continuing air leakage are significant causes of morbidity and mortality. Occasionally, solely conventional techniques such as classical suturing and patch application are not sufficient to stop bleeding, and tissue adhesives, which may be effective across large surfaces, may be helpful [1]. Ethyl 2-cyanoacrylate is one of these tissue adhesives.

In our clinic, we use ethyl 2-cyanoacrylate in cases where hemorrhage cannot be controlled by classical methods and tissue integrity cannot be attained, in cases with sternal dehiscence, and in continuing pulmonary air leakage [2,3]. We use it as a tissue adhesive together with pericardial patch, expanded polytetrafluoroethylene patch (ePTFE, Impra, Inc, Tempe, AZ, USA) or Teflon felt, for repairing the tissues, and we are satisfied with this glue.

In this experimental study, we investigated the histopathological changes in the presence of ethyl 2-cyanoacrylate (Lely Turbo, Henkel Inc., Turbo Kleber, Turbo Klebstoff, Germany) in myocardium, ascending aorta, lung and abdominal aorta of rats. Our aim was to compare histopathological reactions in tissues with glue application and without glue application. We investigated so that

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the results would support our clinical usage of ethyl 2-cyanoacrylate from a histopathological point of view.

2. Materials and methods

Sprague–Dawley rats were used for the demonstration of histological changes in tissues in the presence of ethyl 2-cyanoacrylate. The Marmara University, Animal Care and Use Committee approved the experiments. All animals received humane care in compliance with the European Convention on Animal Care.

2.1. Animals

Male adult Sprague–Dawley rats weighing 250–300 g were kept in a light-controlled room with a 12:12-h light–dark cycle; temperature (22 ± 0.5 °C) and relative humidity (65–70%) were kept constant. They were fed with a standard pellet food and water ad libitum.

2.2. Experimental groups

Four study and four control groups (one for each of the following tissues: myocardium, ascending aorta, lung and abdominal aorta) were used for pathological examinations.

2.3. Anesthesia and preoperative antibiotic prophylaxis

Following 12 h of fasting, all subjects were given intraperitoneal ketamine (100 mg/kg) and chlorpromazine (0.75 mg/kg) for anesthesia. Experiments were carried out under sterile conditions and antibiotic prophylaxis with cefazolin sodium (30 mg/kg intramuscularly, single preoperative dose) was given.

2.4. Artificial respiration

Surgical area was cleansed and draped. Following exploration of trachea, rats were intubated via endotracheal cannulation (16-G Vasofix, B. Braun Melsungen, AG, Germany). Tidal volume and respiratory rate were adjusted to 10 ml/kg (3 ml for an average of 250–300 g subject) and 60 times per minute, respectively. Rodent ventilator (Ugo Basile, Biological Research Apparatus, Comerio, Varesee, Italy) was used for artificial respiration.

2.5. Injury sites for thoracic organs

For interventions on myocardium, ascending aorta and lung, a midsternal incision was used. Sternum was separated by self-retaining retractor to provide adequate exposure (Weitlaner retractors, Medicon Instrumente, Germany). During surgical interventions to these thoracic organs [$n = 36$ for each organ, six subjects for each of six different time points (1st, 7th, 15th, 30th, 45th and 60th days)], in order to prevent the exsanguination of the animal, a purse string suture with 7/0 polypropylene suture material (Sharpoint Ar-Med Ltd, UK) was placed on the anticipated site of injury and then injury (with an approximate size of 4 mm length and 2 mm depth) was made with a no. 11 sterile blade. The sites of injury were right ventricular outflow tract for myocardium, proximal part for ascending aorta, and for the lung it was the middle part of left upper lobe that is reached after the left pleura is opened.

2.6. Ethyl 2-cyanoacrylate and its application

The adhesive substance is a monomer composing of ethyl 2-cyanoacrylate (Lely Turbo, Henkel Inc., Turbo Kleber, Turbo Klebstoff, Germany) and a solvent. The reason for the presence of solvent is to dilute ethyl 2-cyanoacrylate and provide a less viscous solution. The substance is a monomer in its tube, however when it contacts with air and application surface, it polymerizes. Following its application, the substance releases heat to the environment. We do not heat or process the substance before application. We purchase this substance in this form and apply directly. The surgeon puts this substance into a 1 ml syringe and applies directly. This syringe eases the application and the substance can be directed more easily. In our clinical practice, for a surgical site with uncontrolled bleeding, we put additional pledgeted sutures, apply compression and as a last option we use adhesives. The site for adhesive application is not a dry place and bleeding continues as oozing. But we try to provide a relatively dry environment by using compression and pledgets. The substance may not be useful in active and copious amounts of bleeding, as active bleeding prevents the adherence and decreases the effectiveness of the substance.

2.7. Application of ethyl 2-cyanoacrylate to ascending aorta, myocardium, and lung

In order to prevent exsanguination of the animal due to hemorrhage caused by the injury made on ascending aorta and myocardium, purse string suture was slightly retracted upwards and when bleeding is in the form of oozing an ePTFE patch was adhered to the site of injury by ethyl 2-cyanoacrylate [approximately 6.2–6.4 mg (one small drop)]. Hemorrhage was not observed in any of the two organs after the procedure. For lung, the same dose of ethyl 2-cyanoacrylate and ePTFE patch was applied to the site of injury with air leakage. Following the procedure, no air leakage was observed. For all three organs, purse string sutures placed for safety were not tied and in order not to disturb the relation of tissue adhesive with the tissue during removal, they were left in place. During closure, air in the mediastinal and thoracic cavities was emptied by a drainage cannula (16-G Vasofix) inserted at the level of lower tip of xiphoid and a three-way stopcock system;

the drainage cannula was removed while tying the last suture. Then the rats were extubated.

2.8. Application of ethyl 2-cyanoacrylate to abdominal aorta

For the fourth group (abdominal aorta group, $n = 36$, six subjects for each of six different time points), abdominal aorta was surgically reached via median abdominal incision under general anesthesia and without intubation, then abdominal aorta was surgically prepared. First, a safety suture was placed on the anticipated site of aortotomy with a 7/0 polypropylene suture material. Then partial abdominal aortotomy was done while there is proximal and distal clamps (Vascu-Statt, bulldog clamp, Netherlands), then ePTFE patch was adhered to the site of aortotomy by ethyl 2-cyanoacrylate. No hemorrhage was observed following declamping and purse string suture was left in place untied.

2.9. Control groups

For the control groups, injury sites in myocardium, ascending aorta, lung and abdominal aorta were closed by suturing with 7/0 polypropylene suture material, without applying ethyl 2-cyanoacrylate (groups 1a, 2a, 3a and 4a; for each organ $n = 36$, six subjects for each of six different time points).

2.10. Preparation and evaluation of pathological specimens

Following sufficient depth of general anesthesia, organs in which surgical intervention was performed were en bloc removed (only one organ was removed from each subject) at six specified time points. All specimens were transported in 10% buffered formaldehyde solution. After 48 h of fixation, three cross sections were taken from the arteriotomy specimen; one from the middle part of the patch that is just at the level of the arteriotomy and one from 2 mm proximal and one from 2 mm distal to the arteriotomy. For lung and heart, two sections were taken from the incision line. Histopathological sections were prepared in transverse plane. Each section had 5 μm thickness. All sections were stained with hematoxylin-eosin (HE) and arteriotomy sections from the 15th and 60th day were also stained with Elastic van Gieson (EVG). Arteriotomy sections 45th day were also stained immunohistochemically with factor VIII-related antigen (Neomarkers, Inc, RB-281-R7, Fremont, USA). All sections obtained at 30th and 60th days were also stained with Oil-Red-O (ORO).

2.11. Light microscopy findings

Light microscopy findings were graded as 0 to +3 which corresponds to no change, mild, moderate and severe changes, respectively. Assessments were made for inflammatory reactions, necrosis, endothelial cell loss, aneurysm formation, intimal hyperplasia, new vessel and connective tissue formation in tissues. Medial necrosis was evaluated by ocular eyepiece micrometer (Olympus eyepiece micrometer, U-OCMC10/100XY) in arteriotomy sections of the first day.

2.12. Statistical analysis

Statistical analyses were performed using SPSS 10.0 (SPSS Inc., Chicago, IL), MATLAB 6.0.88 release 12 (MATrix LABoratory, The MathWorks, Inc., Boston, MA), NCSS (Number Crunching Statistical Software, Kaysville, UT) and PASS 2000 (Power Analysis and Sample Size, Kaysville, UT) statistical programs. Data are expressed as mean ± standard deviation. A P-value <0.05 was considered to indicate statistical significance.

For the six specified different time points, mean pathological changes observed in four different tissues were evaluated by using Hotelling's T^2 test among study and control groups. For the significance of T^2 test statistics, F distribution was used. For the homogeneity of dispersion matrixes of variables across groups, Barlett's χ^2 test was used.

According to these results, for each of the four organ groups, there was no statistically significant difference between the two groups. To investigate the mean difference of pathological changes across groups, confidence intervals were calculated by using the Bonferroni approach. Obtained results were not significant ($P > 0.05$).

3. Results

In histopathological analysis of vascular, myocardial and pulmonary tissue sections, there was no significant histopathological difference between conventionally sutured tissues (control group) and ethyl 2-cyanoacrylate-applied tissues (study groups; Figs. 1–4). Findings for tissue samples from the study group are demonstrated in Table 1.

3.1. Microscopic findings: ascending aorta

There were no significant differences between the groups in terms of medial necrosis at the first day (study group 0.025 mm^2 vs. control group 0.022 mm^2). Intimal hyperplasia at the site of arteriotomy was lesser in the control group compared to the study group at days 15 and 30. Both groups had endothelial cell regeneration at day 45 and regenerated elastic membranes at the site of arteriotomy at day 60.

3.2. Microscopic findings: abdominal aorta

There were no significant differences between the groups in terms of medial necrosis at the first day (study group 0.015 mm^2 vs. control group 0.021 mm^2). In both groups,

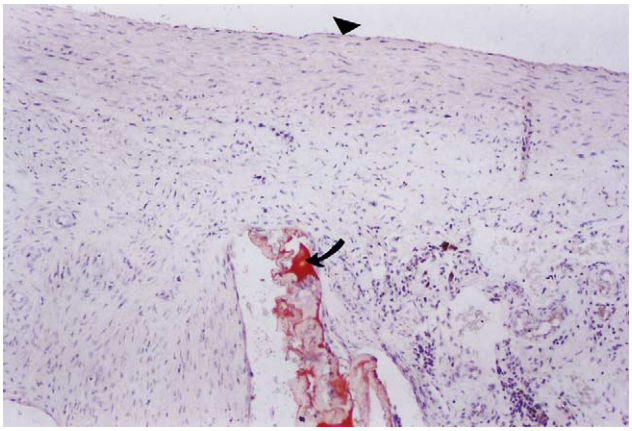

Fig. 1. Histological examination of ascending aorta at the 60th day: minimal lymphocytic infiltration around cyanoacrylate (arrow), which is stained red by Oil-Red-O staining. Note the lining of luminal surface without intimal hyperplasia (arrowhead) (Oil-Red-O, × 100).

there was disruption of elastic fibers at the site of arteriotomy at day 15, endothelial cell regeneration at day 45 and regeneration of elastic membranes at day 60.

3.3. Microscopic findings: myocardium

Acute inflammatory cell infiltration around the incision line was more prominent in the control group at the 1st and 7th days. At day 30, early fibroid tissue and new vessel formation were more prominent in the study group. At day 60, both groups had connective tissue with numerous new small blood vessels.

3.4. Microscopic findings: pulmonary

Necrosis and acute inflammatory reaction were less prominent in the control group at the 1st and 7th days. In both groups, there was fibrous tissue formation at day 30

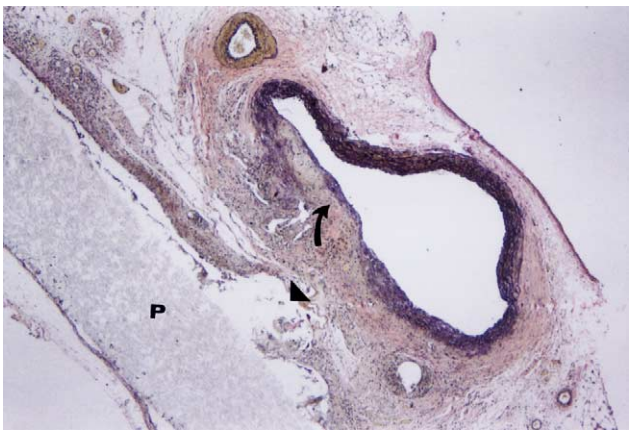

Fig. 2. Histological examination of abdominal aorta at the 15th day: the arteriotomy gap is filled by repair tissue formed by vascular smooth muscle cell proliferation (arrow). Cyanoacrylate is seen as empty spaces (arrowhead) between patch and vessel wall (Elastic van Gieson, × 40) (P, patch).

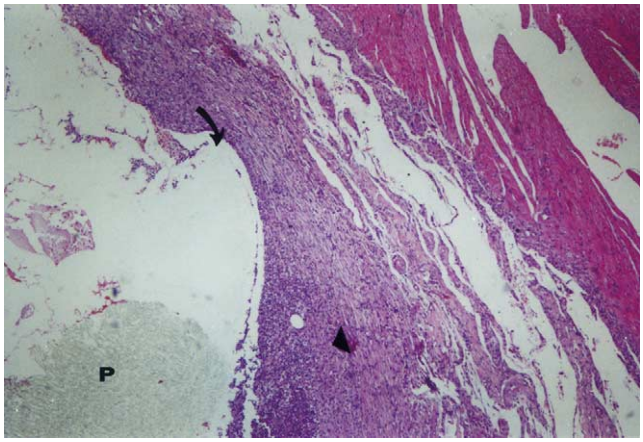

Fig. 3. Histological examination of myocardium at the 15th day: inflammatory exudate (arrowhead) consisting of polymorphonuclear leucocytes, lymphocytes and early fibrous tissue is seen adjacent to the patch and empty spaces (arrow) that contain cyanoacrylate (hematoxylin-eosin, × 40) (P, patch).

and connective tissue formation with new small blood vessels at day 45.

4. Discussion

Cyanoacrylate derivatives are among tissue adhesives, which may be used in cardiovascular and pulmonary surgery when necessary [1,4–7]. According to the comparative trials with biological adhesives, cyanoacrylate may be complementary for or alternative to classical suture technique due to its strong bonding upon application, despite its low elasticity [8].

We used ethyl 2-cyanoacrylate for the first time in a right ventricular injury that could not be repaired adequately by conventional suture technique. We thought that a tissue

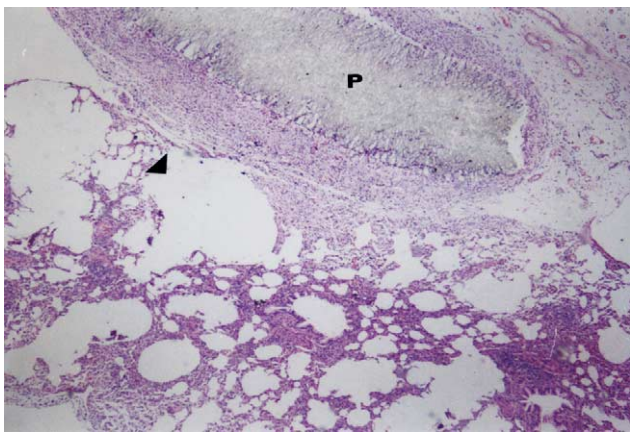

Fig. 4. Histological examination of pulmonary tissue at the 30th day: polymorphonuclear leucocytes, lymphocytes, infiltration of few giant cells with numerous newly formed blood vessels in early fibrous tissue. Arrowhead indicates empty space that was containing cyanoacrylate (hematoxylin-eosin, × 40) (P, patch).

Table 1
Microscopic findings in ethyl 2-cyanoacrylate-applied tissues

	Ascending aorta	Abdominal aorta	Myocardium	Pulmonary
1st day	Acute inflammatory reaction. Minimal endothelial cell loss. Medial layer necrosis.	Acute inflammatory reaction. Minimal endothelial cell loss. Medial layer necrosis.	Acute inflammatory reaction. Minimal myocardial fiber necrosis.	Acute inflammatory reaction. Minimal coagulation necrosis.
7th day	Acute inflammatory reaction. Smooth muscle cell proliferation at the arteriotomy site. Minimal medial necrosis.	Acute inflammatory reaction. Vascular smooth muscle cell proliferation at the arteriotomy site. Minimal medial necrosis.	Increased acute inflammatory reaction. Minimal myocardial fiber necrosis.	Acute inflammatory reaction. Minimal necrosis and hemorrhage.
15th day	Acute and chronic inflammatory reaction. Fragmentation of elastic fibers[a]. Minimal intimal hyperplasia.	Acute and chronic inflammatory reaction. Fragmentation of elastic fibers[a]. Repair tissue formation.	Acute and chronic inflammatory reaction. Minimal myocardial fiber necrosis. Early fibrous tissue with newly formed small blood vessels.	Decreased acute inflammatory reaction. Early fibrous tissue formation.
30th day	Acute and chronic inflammatory reaction. Small amounts of foreign body giant cells. Minimal intimal hyperplasia.	Decreased acute inflammation. Small amounts of foreign body giant cells. Increased lymphocytic cell infiltration. Fibroblastic proliferation in adventitial layer. Minimal intimal hyperplasia.	Lymphocytic infiltrate with foreign body giant cells. Minimal myocardial fiber necrosis. Increased amount of fibrous tissue with numerous small blood vessels.	Lymphocytic infiltration with foreign body giant cells. Fibrous tissue formation.
45th day	Decreased acute inflammation. Endothelial cell regeneration[b].	Endothelial cell regeneration[b].	Connective tissue formation.	Connective tissue formation with new small blood vessels.
60th day	Minimal chronic inflammation. No medial necrosis. No intimal hyperplasia. No aneurysm or thrombus formation. Cyanoacrylate still present[c].	Minimal chronic inflammation. Minimal foreign body reaction. No medial necrosis. No Intimal hyperplasia. No aneurysm or thrombus formation. Cyanoacrylate still present[c].	Minimal lymphocytic infiltrate. Connective tissue with numerous new small blood vessels. No giant cell. No thrombus or excessive scar formation. Cyanoacrylate still present[c].	More prominent connective tissue formation. Cyanoacrylate still present[c].

[a] EVG staining revealed fragmentation of elastic fibers.
[b] Immunohistochemical staining by using factor VIII-related antigen demonstrated endothelial cell regeneration.
[c] Oil-Red-O stain showed that cyanoacrylate was still present in the tissue.

adhesive could be helpful and used it in an emergency situation and got a good result. Reasons why we currently use this substance are that it is effective, may be life saving, inexpensive, easily accessible and easily applicable, and we are satisfied with the outcomes. The operations in which we used ethyl 2-cyanoacrylate as a tissue adhesive for repairing the tissues were as follows: in thoracic aortic surgery when there is need to support anastomotic line or aortotomy (22 patients), in redo sternotomy when laceration of right ventricular free wall occurs during dissection (9), after resection of left ventricular aneurysm (4), bleeding from proximal anastomosis during coronary bypass surgery (4), bleeding following left ventriculotomy performed for hydatid cyst (1), in superior vena cava laceration (1) and in rupture of coronary sinus (1), in sternal dehiscence (16), in continuing pulmonary air leakage (5), and bleeding from femoral artery due to femoral epidermoid carcinoma (1 patient). Ethyl 2-cyanoacrylate application was successful in 61 patients (95.3%).

When we fail to provide sternal integrity by the use of wires during primary or secondary revisions due to sternal dehiscence, following wire application we apply ethyl 2-cyanoacrylate between two edges and then approximate the edges.

Jacobson and colleagues [9] applied cyanoacrylate to dogs for vascular anastomosis and reported that an acute reaction was developed after 12 h, necrosis in the media was observed after 72 h, necrotic site of media was covered with fibroblasts after 4 days, necrotic media was completely renewed by fibrous tissue after 3 months, and after 6 months both media and intima were normal except for chronic inflammation at the suture site. Also in our study, in tissues

where ethyl 2-cyanoacrylate was used for vascular anastomosis, acute inflammatory response and medial necrosis were prominent during the first week, however, after the second week repair tissue filling the arteriotomy site, composed of smooth muscle cells, and chronic inflammatory response were prominent. Factor VIII staining revealed at the 45th day that endothelial cell regeneration occurred and this tissue adhesive has no histotoxic effect on the healing of arteriotomy site. At the end of the second month, completion of the regeneration of internal and external elastic membranes provides vascular continuity. Lack of intimal hyperplasia, aneurysm or thrombus formation supports Chen and colleagues' [10] suggestion that thrombus formation may be related to technical issues rather than cytotoxicity. Bastiaanse and colleagues [8] reported that no medial dissection, necrosis, thrombus or vascular deformity was found in the carotid artery tissue of pigs to which cyanoacrylate was applied.

It is reported in the literature that inflammation following the application of cyanoacrylate to the vessels with a diameter of 0.5–2 mm resulted in intimal hyperplasia, aneurysm and thrombus formation and it is stated that it should not be applied to vessels with a diameter <2 mm [11]. However, in our study the diameters of vessels where we applied cyanoacrylate ranged between 0.7 and 1.3 mm, but no thrombus or aneurysm formation was observed. Minimal intimal hyperplasia was detected at the first month, but at the end of the 2 months it also disappeared.

In our study, no significant histopathological difference was found between the myocardial samples of cyanoacrylate-applied rats and conventionally sutured rats at the end of 2 months, demonstrating that ethyl 2-cyanoacrylate does not have any unfavorable effect on myocardial wound healing. A rapid and effective solution for pulmonary air leakage is possible occasionally by the use of tissue adhesives. In the rats where we applied ethyl 2-cyanoacrylate over the lungs, a good adhesion was provided despite the relatively mobile nature of the lung, and excessive necrosis and scar tissue was not formed, all suggesting that ethyl 2-cyanoacrylate may be applied to the lung. We did not observe any 'foreign body type granulomatous reaction' in the tissues where we applied cyanoacrylate; we found foreign body type giant cells only as much as the conventional suture group. These findings show that ethyl 2-cyanoacrylate is compatible with tissues. In the study of Toriumi and colleagues [12], demonstration of biochemical degradation of ethyl 2-cyanoacrylate suggests that it will not persist in the tissue.

5. Conclusions

In conclusion, according to our experimental study and in the light of our previous clinical experience, we suggest that ethyl 2-cyanoacrylate may be used in cardiovascular and pulmonary surgery, as an alternative or adjunct to conventional techniques in controlling hemorrhage that cannot be controlled by conventional methods, in tissue repair, and in the control of pulmonary air leakage. As a tissue adhesive, it has the advantages of being inexpensive, readily available, easily applicable, effective, safe, and life saving. Due to its acceptable histopathological results, ethyl 2-cyanoacrylate may be used as an alternative adhesive, which may be effective on large surfaces in surgical interventions where tissue integrity cannot be provided.

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