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Histopathological Examination of Cyanoacrylate Usage in Cartilage Graft Fixation

ABSTRACT

Background: The aim of this study is to investigate the histopathological effects of 2-octyl-cyanoacrylate used in facial plastic operations that are applied for the fixation of cartilage graft types and the graft stabilization effect.

Methods: In the study, 16 New Zealand-type rabbits weighing between 2250 g and 2500 g, 3-4 months old, were used. Two groups were formed as the study and control groups. Those using 2-octyl-cyanoacrylate for cartilage graft fixation were defined as the study group. Those using suturing were defined as the control group. The operation was planned with cartilage grafts taken from the ears of each rabbit and the study group on the left of the sagittal suture and the control group on the right.

Results: Acute inflammation findings were found in 19 (39.6%) of the study group and 6 (14%) of the control group. Acute inflammation levels were found to be higher in the study group than in the control group ($P = .006$). Mild inflammation was found in 20 (41.7%) of the study group, moderate inflammation in 7 (14.6%), and severe inflammation in 2 (4.2%). Mild inflammation was detected in 10 (23.3%) of the control group. Chronic inflammation levels were higher in the study group than in the control group. Foreign body reaction was detected in 28 (58.3%) of the study group and 14 (32.6%) of the control group. Foreign body reaction levels were found to be higher in the study group than in the control group.

Conclusion: We think that the use of 2-octyl-cyanoacrylate in cartilage graft fixation is not correct as it may increase the risk of postoperative complications.

Keywords: Cyanoacrylate, 2-octyl-cyanoacrylate, cartilage graft, animal study, rabbit, tissue adhesive

INTRODUCTION

Cartilage grafts are used in many facial plastic surgery operations such as auricular reconstruction, nasal reconstruction, and reconstruction of facial bone depressions.[1-3] In many esthetic surgical operations such as septorhinoplasty, cartilage grafts are used to achieve fullness and correct the deteriorated contour. Cartilage grafts can be used as crushed or chopped without any procedure, but the use of cartilage grafts has complications such as resorption, infection, and graft removal, albeit at a low rate.[4]

Stabilization of cartilage grafts is usually provided with sutures. Fixing small and thin pieces of cartilage is inconvenient and time-consuming. In addition, technical difficulties and infection risks may increase when more than 1 cartilage layer is sutured. The use of tissue adhesives can create an alternative method to these processes.[5]

Tissue adhesives are used quite often in practice.[6] Cyanoacrylates, on the other hand, have been used as synthetic tissue adhesives in clinical practice for a very long time. Cyanoacrylates are used in a wide range of surgeries such as bone reconstruction, laryngeal repair, rhinoplasty, blepharoplasty, dental procedures, transcatheter arterial embolization, and corneal perforation repair.[7-13] These adhesives polymerize rapidly as soon as they come into contact with the surface and form strong and flexible bonds.[14] Their biocompatibility directly depends on the histotoxicity they can create. Their histotoxicity is due to formaldehyde and cyanoacetate formed during their decomposition. Long-chain cyanoacrylates make this decomposition reaction much slower. Thus, less toxic

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effects are observed in the tissue.[15] The 2-octyl-cyanoacrylate (2-OCA) is the newest and longest chain form of cyanoacrylate. Its breaking strength is 3 times higher than that of *N*-butyl-cyanoacrylates and it is equivalent to 5/0 nylon sutures in terms of strength.[16]

The 2-OCA is one of the most widely used tissue adhesives in the world. Food and Drug Administration approval was granted in 1998. Indications of 2-OCA include surgical incision closure, closure of clean lacerations, and closure of deep or high-tension wounds with subcutaneous sutures. Definite contraindications of 2-OCA are gangrenous wound, active infection site, and decubitus ulcer. The other definite contraindication is patients with a history of cyanoacrylate or formaldehyde hypersensitivity reaction. In addition, its use is not recommended for those with peripheral vascular disease, clotting disorders, insulin-dependent diabetes mellitus, and patients with a history of keloids in themselves or their family.[14]

The aim of this study is to investigate the histopathological effects of 2-OCA used in facial plastic operations that are applied for the fixation of cartilage graft types and the graft stabilization effect.

MATERIAL AND METHODS

In the study, 16 New Zealand-type rabbits aged 3-4 months, weighing between 2250 g and 2500 g, were used. All animals included in the study were housed in standard laboratory conditions with a temperature of 22 ± 2°C, with humidity maintained at 60%-70% and with 12-h light–12-h dark periods. All animals were fed standard rabbit food and water in their cages. No restrictions were applied to the animals throughout the study. The approval of the ethics committee of the study was obtained from the Ümraniye Training and Research Hospital Ethics Committee of Experimental Animals (Ethics Committee Approval No: 2019/122 and Date: 07.05.2019).

Two groups were formed as study and control groups. Those who used 2-OCA for cartilage graft fixation were defined as the study group. Those who used sutures were defined as the control group. The operation was planned in such a way that the cartilage grafts taken from the ears of each rabbit were the study group on the left side of the sagittal suture in the skull and the control group on the right side.

MAIN POINTS

- Cartilage grafts are used in many facial plastic surgery operations.
- Stabilization of cartilage grafts is usually provided with sutures.
- The use of tissue adhesives can be an alternative method to sutures.
- 2-Octyl-cyanoacrylate (2-OCA) is the newest and longest chain form of cyanoacrylate.
- Although 2-OCA is more practical than sutures, it has more complications than sutures.

Experimental Groups

The 2 groups are divided into 3 subgroups. Subgroups were designed as follows: (A) pure cartilage graft, (B) crushed cartilage graft, and (C) chopped cartilage graft. Cartilage grafts taken from the left ear of rabbits were used to the left side of the sagittal suture, while those taken from the right ear were used to the right side of the sagittal suture. The cartilage grafts were obtained from the auricula of rabbits. The measurements of the grafts were made precisely and 6 cartridge grafts with dimensions of 5 × 5 mm were obtained. All grafts were treated in accordance with the subgroup.

After obtaining the cartilage graft material from the left ear of rabbits in each subgroup of the study group, it was placed on the left of the sagittal suture according to the reference point.

By gluing 1A pure cartilage graft with 2-OCA to the left side of the sagittal suture line in the 2-OCA subgroup, bone-cartilage graft fixation was obtained.

By gluing 1B crushed cartilage with 1-OCA crushed cartilage in the 2-OCA subgroup to the left side of the sagittal suture line, graft-bone-cartilage graft fixation was obtained.

By sticking the 1C chopped cartilage with 2-OCA to the chopped cartilage from 2-OCA subgroup to the left side of the sagittal suture line, bone-cartilage graft fixation was obtained.

After obtaining cartilage graft material from the right ear of rabbits in each subgroup of the Control group, it was placed on the right side of the sagittal suture line according to the reference point.

In the 2A pure cartilage-control subgroup, bonecartilage fixation was achieved by suturing to the right of the graft sagittal suture line.

Bonecartilage fixation was achieved by suturing the crushed cartilage in the 2B crushed cartilage-control subgroup to the left side of the sagittal suture.

In the 2C chopped cartilagecontrol subgroup, the chopped cartilages were placed on the right side of the sagittal suture line by creating a subperichondrial pocket.

Surgical Procedure

Anesthesia of the subjects was provided by intramuscular injections of 55 mg/kg "ketamine hydrochloride" (Ketalar™) and 5 mg/kg "xylazine hydrochloride" (Rompun™ HCl 2%). Following anesthesia, the ears and head area of the subjects were cleaned of hair and a hairless surgical field was obtained. The surgical area was washed with an antiseptic solution and covered with a sterile drape.

After injecting lidocaine under the skin of the dorsomedial part of the ear of the subject, a vertical incision of approximately 4 cm was made. After reaching the cartilage layer, bilateral perichondrium elevation was performed. A 30 × 30 mm graft was obtained from the ear. The donor area skin of the ear was closed by primary suturing with a 4/0 cutting needle polyglactin dissolving suture. Grafts of 5 × 5 mm sizes were prepared from the taken cartilage graft material. These grafts were applicable to the protocol of the subgroup to which they would be applied.

Grafts were not processed for groups A. For groups B, crushing was performed with a cartilage crusher. For groups C, chopping was done with a No. 11 scalpel.

A 6 cm long vertical incision was made on the sagittal suture line extending from the frontal bone to the occipital bone in the dorsal region of each rabbit's head. In order to calculate the places where the created cartilage grafts will be fixed, a decisive suture was placed at a point on the sagittal suture line with a 4/0 sharp needle propylene non-absorbable suture. Grafts were placed according to this point and sagittal suture line.

Grafts in group 1A were fixed with 2-OCA 10 mm posterior to the defining suture and 10 mm left lateral of the sagittal suture line. Grafts in group 1B were fixed with 2-OCA 10 mm posterior to the graft in group 1A and 10 mm left lateral to the sagittal suture line. Grafts in group 1C were fixed with 2-OCA in group 1B and 10 mm posterior to the graft. It was fixed 10 mm left lateral to the sagittal suture line with 2-OCA. Grafts in group 2A were fixed with absorbable 5/0 round needle polydioxanone suture 10 mm posterior to the defining suture and 10 mm right lateral to the sagittal suture line. Grafts in group 2B were fixed with absorbable 5/0 round needle polydioxanone suture 10 mm posterior to the graft in group 2A and 10 mm right lateral to the sagittal suture line. Grafts in the group 2C were placed 10 mm posterior to the graft in the 2B group and 10 mm right lateral to the sagittal suture line by opening a subperichondrial pocket, and the pocket was closed with a 5/0 round needle polydioxanone suture.

After the graft placement process was completed, the skin of the incision line was closed by primary suturing with a 4/0 cutting needle polyglactin suture.

After the completion of the surgery, the subjects were followed for 6 and 12 weeks postoperatively. During this period, none of the subjects developed complications at the wound site. The incision lines of all subjects healed uneventfully.

At the end of the 6- and 12-week periods, the lives of 8 subjects at a time were terminated with high-dose anesthetic. After the hairs in the head area were cut, an incision was made on the surgical site from the previous incision line. The skin in this area was excised for better visualization of the grafts. Necessary measurements and photographs were taken for the determination of the migration of the grafts. Then, the graft material of each subgroup was excised together with the fixed bone tissue. The excised bone and cartilage graft junction were fixed in 10% neutral buffered formalin. After the fixation process, the tissues that underwent tissue follow-up (Leica TP 1020, Nussloch, Germany) were decalcified with 10% formic acid for 2-3 hours. Paraffin blocks were prepared from these tissues, and sections of 4 μm were taken from these blocks, and the sections were stained with hematoxylin–eosin (H&E) and examined by a specialist pathologist under the light microscope (Olympus Cx41) with a single-blind method.

Statistical Analysis

While evaluating the findings obtained in the study, IBM Statistical Package for the Social Sciences Statistics version 23.0 program (IBM corp., Armonk, NY, USA) was used for statistical analysis. If the data exhibits a normal distribution, it was calculated as mean ± SD; if it does not conform to a normal distribution, it was calculated as median (minimum–maximum). The categorical variables were shown as n (%). Kolmogorov–Smirnov test was used to assess the normality of the distribution. Pearson's chi-square and Fischer's exact tests were used to compare histopathological data. "Fisher–Freeman–Halton test" has been used in tables larger than 2×2 that have a problem of expected value. In our study, the type 1 error level was accepted as .05.

RESULTS

While no signs of acute inflammation were found in 29 (60.4%) of the study group, 19 (39.6%) were found to have signs of acute inflammation (Figure 1). In the control group, 37 subgroups (86%) did not have acute inflammation findings and 6 (14%) had acute inflammation findings. Acute inflammation levels were found to be higher in the study group than in the control group ($P = .006$) (Table 1).

It was determined that 19 (39.6%) of the study group did not have chronic inflammation, 20 (41.7%) had mild inflammation, 7 (14.6%) moderate, and 2 (4.2%) had severe inflammation. In the control group, 33 (76.7%) had no chronic inflammation and 10 (23.3%) had mild inflammation (Figure 2). Chronic inflammation levels were higher in the study group than in the control group (Table 2). There was no statistically significant difference between the subgroups of the study group (Groups 1A-1B-1C) in

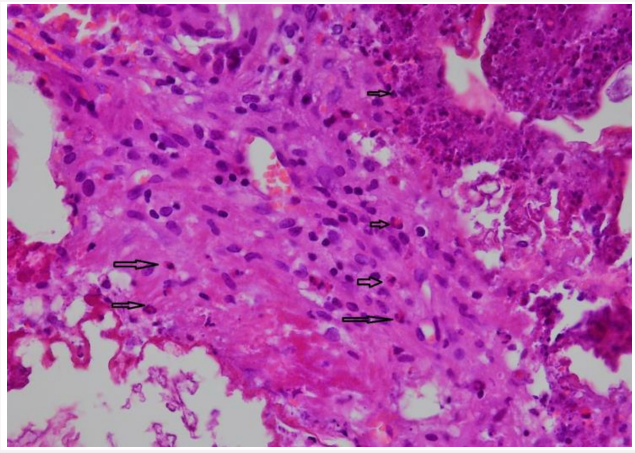

Figure 1. Acute inflammation (hematoxylin–eosin) (×400).

Table 1. Comparison of Acute Inflammation Between Study and Control Groups

			Study Group	Control Group	Total	*P*
Acute inflammation	Yes	n	29	37	66	**.006***
		%	60.4%	86.0%	72.5%	
	No	n	19	6	25	
		%	39.6%	14.0%	27.5%	
Total		n	48	43	91	
		%	100.0%	100.0%	100.0%	

It indicates the p-value. It is written in bold to signify its statistical significance.
The asterisk (*) in Table 1 is used to represent the p-value.

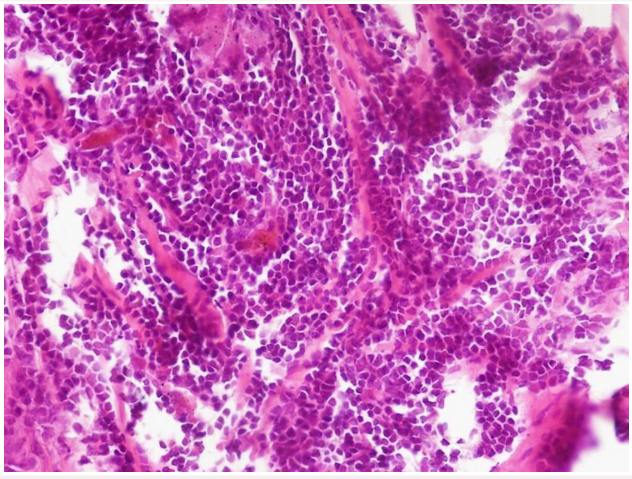

Figure 2. Chronic inflammation (hematoxylin–eosin) (×400).

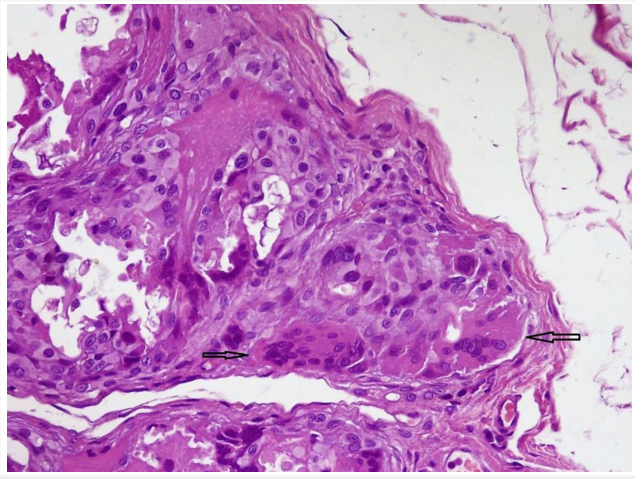

Figure 3. Foreign body giant cells (hematoxylin–eosin) (×100).

Table 2. Comparison of Chronic Inflammation Between Study and Control Groups

			Study Group	Control Group	Total	*P*
Chronic inflammation	None	n	19	33	52	**<.01**
		%	39.6%	76.7%	57.1%	
	Mild	n	20	10	30	
		%	41.7%	23.3%	33.0%	
	Moderate	n	7	0	7	
		%	14.6%	0.0%	7.7%	
	Severe	n	2	0	2	
		%	4.2%	0.0%	2.2%	
Total		n	48	43	91	
		%	100.0%	100.0%	100.0%	

It indicates the p-value. It is written in bold to signify its statistical significance.

Table 3. Comparison of Foreign Body Reaction

		Study Group	Control Group	Total	*P*
Foreign body reaction	n	20	29	49	**.014***
	%	41.7%	67.4%	53.8%	
	n	28	14	42	
	%	58.3%	32.6%	46.2%	
Total	n	48	43	91	
	%	100.0%	100.0%	100.0%	

It indicates the p-value. It is written in bold to signify its statistical significance.
The asterisk (*) in Table 3 is used to represent the p-value.

the evaluation of chronic inflammation ($P = .703$). There was no statistically significant difference between the subgroups of the control group (Groups 2A-2B-2C) in the evaluation made in terms of chronic inflammation ($P = .633$).

It was determined that 20 (41.7%) of the study group did not have a foreign body reaction and 28 (58.3%) had a foreign body reaction (Figure 3). It was determined that 29 (67.4%) of the control group did not have foreign body reactions and 14 (32.6%) had foreign body reactions. Foreign body reaction levels were found to be higher in the study group than in the control group (Table 3).

DISCUSSION

Cartilage graft is frequently used in facial deformity repairs, especially in septorhinoplasty operations.[17] It is possible that cartilage grafts may lead to undesirable functional and esthetic results in the immediate or long-term postoperatively following their use during the operation.[4] For this reason, it is extremely important to use the cartilage graft with the most ideal technique and method. Cartilage grafts can be used as they can be left free to the area where they will be placed or they can be fixed to the surgical area. The most common suture material is preferred for cartilage graft fixation. Fixation of cartilage grafts to bone structures is a challenging procedure that prolongs the surgical time. There are also limitations and surgical difficulties brought about by the use of sutures in the shaping process.[18] For this reason, studies are carried out to facilitate and accelerate the cartilage graft shaping process. In order to make the aforementioned difficulties easier, the use of tissue adhesives comes to the fore.

Cyanoacrylate is used for graft fixation by many branches along with otorhinolaryngology and plastic surgery.[19-22] The main questionable part of the use of cyanoacrylate during surgical procedures is possible histotoxic effects such as inflammation, foreign body reaction, and tissue necrosis.[23] Histotoxic effects are related to the amount of adhesive used, the vascularization of the applied tissue, the heat generated during polymerization, and the concentration of degradation products produced during depolymerization.[24] Considering these effects, only long-chain monomer cyanoacrylate derivatives are used as tissue adhesives. The longer the chain molecule, the longer the depolymerization time. Thus, less toxic effects are observed in the tissue. 2-Octyl-cyanoacrylate is the cyanoacrylate derivative with the longest chain ever produced and is one of the most widely used tissue adhesives in the world.[14] For this reason, 2-OCA was used in our study.

The 6-week follow-up period of a 3-month-old rabbit is considered to be 2 years in human life, and the equivalent of a 12-week follow-up period is 6 years.[25] This study used a 6-week follow-up to examine short-term effects and a 12-week follow-up to examine long-term effects.

Standlee and Hohman[26] used 2-OCA to fix the spreader graft in 108 patients who underwent rhinoplasty. Inflammation findings were observed in 12 (11%) of the patients. Abscess developed in 3 (3%) patients and required surgical revision.[26] Similarly, Gall et al[27] had to perform surgery in 2 of their patients who developed a septal abscess. Min and Jang[5] used 2-OCA for fixation of nasal tip graft in 33 patients who underwent open technique rhinoplasty. Complications developed in 24% of the patients, including erythema in 9.1%, infection in 12.1%, and esthetic dissatisfaction in 3.0%. In their study with 12 rabbits, Tourimi et al[28] observed moderate acute inflammation in the use of cyanoacrylate for fixation between the bone graft and cartilage in the nonvascularized area. They observed more severe inflammation with cyanoacrylate in the vascularized soft tissue region. They also encountered more foreign body reactions in the use of cyanoacrylate.[29] Esteves et al.[30] in their study on 48 rats, showed that fixation of bone graft material to bone tissue with 2-OCA resulted in a higher short- and long-term inflammatory reaction compared to the control group. In our study, acute and chronic inflammation findings were found to be higher in the study group than in the control group. There was no difference between the subgroups of the study and control groups in terms of acute and chronic inflammation. Different procedures applied to the cartilage do not seem to be a determining factor in inflammation. The use of 2-OCA seems to be the main factor that increases inflammation. These findings in our study support the data in the literature.

In our study, the reason for the higher incidence of inflammation and foreign body reactions in 2-OCA groups compared to the control groups is that although the amount of cyanoacrylate used is very small, it is difficult to prevent its spread to the surrounding tissues and because the skin is in contact with the graft, it is mainly due to the direct contact of a well-blooded structure with cyanoacrylate. We think that the increased foreign body reaction, especially in the 2-OCA-chopped cartilage group compared to the control-chopped cartilage group, is due to the increase in the skin contact surface with 2-OCA and the use of the amount more to keep the chopped cartilage pieces together in beer.

There are some limitations of this study. First, instead of the nasal septum made of hyaline cartilage, ear cartilage consisting of elastic cartilage was used. Since the latter is a study conducted in rabbits, it should be supported by studies to be conducted in humans.

CONCLUSION

Although 2-OCA may seem easy and practical to use in cartilage graft fixation, it may spread to unwanted areas in the surgical area and cause inflammation and foreign body reaction. For this reason, we think that its use in cartilage graft fixation is not correct, as it may increase the risk of complications after surgery.

Ethics Committee Approval: This study was approved by the Ethic committee of Ümraniye Training and Research Hospital (Approval no: 2019/122, Date: 07.05.2019).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – B.E, A.Ş.Y, M.S.; Design – B.E, İ.D., M.S.; Supervision – A.Ş.Y, İ.D., M.S.; Resources – Y.K.D., Ş.Ş.; Materials – Y.K.D., B.E., Ş.Ş.; Data collection – F.B., T.U., A.N.İ.; Analysis – A.M.T., Ş.Ş.; Literature search – F.B., T.U., A.N.İ.; Writing – B.E., İ.D.; Critical review – A.M.T., İ.D., A.Ş.Y.

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