Original Article

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Effects of Fibrin Glue, 2-Octyl Cyanoacrylate, and N-Butyl Cyanoacrylate on Cartilage Healing: An Experimental Animal Study

Deniz Hanci, Huseyin Altun*, Onur Ustun**, Dilara Zeybek***, Berk Gurpinar, Yavuz Uyar

University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital, Clinic of Otorhinolaryngology, Istanbul, Turkey

**Yunus Emre Hospital, Clinic of Otorhinolaryngology, Istanbul, Turkey*

***University of Health Sciences Turkey, Haseki Training and Research Hospital, Clinic of Otorhinolaryngology Istanbul, Turkey*

****Hacettepe University Faculty of Medicine, Department of Histology and Embryology, Ankara, Turkey*

Abstract

Aim: Following septoplasty surgery, nasal packing is performed to stabilize the healing of septum and prevent septal hematoma. The purpose of this study was to investigate the efficacy of fibrin glue, 2-octyl cyanoacrylate, and n-butyl cyanoacrylate on the healing of the septum cartilage following septoplasty.

Methods: Since rabbit ear cartilages resemble septal cartilage, 10 New Zealand rabbits were used in our study which was performed between March and May 2016. A total of 20 ears of 10 rabbits were used, with 4 separate incisions in each ear. Perichondrial flaps were raised and the following chemical adhesives were applied separately on the cartilage: Fibrin glue, 2-octyl cyanoacrylate, n-butyl cyanoacrylate. As the control group, no material was applied to the remaining incision. The right ears were examined at 15 days and the left ears at 30 days; samples were removed with solid tissue around the edges, treated with formol and histopathologically examined.

Results: Epithelial integrity and re-epithelialization were adequate in all groups. As the epithelium and perichondrium thicknesses were compared in the 15-day samples, epithelium and perichondrium were thicker in the n-butyl cyanoacrylate and 2-octyl cyanoacrylate groups than the other groups.

Conclusion: N-butyl cyanoacrylate, fibrin glue and 2-octyl cyanoacrylate are potential alternatives for cartilage and mucosal support.

Keywords: Cartilage, fibrin tissue adhesive, octyl 2-cyanoacrylate, cyanoacrylates

Introduction

Septoplasty is among the most common operations in otolaryngology. Primarily the mucoperichondrial and mucoperiosteal flaps are elevated and the deviated parts of the cartilage and/or bony septum are repositioned or resected. Following septal surgery, internal nasal packing is applied to stabilize the septum and to prevent septal hematoma, as well as to support septal flap and remove the dead space between the subperichondrial flaps and cartilage (1). If the internal packing of the nose is not adequately provided, bleeding, septal hematoma, perforation, septal instability, septal synechia, infection and a septal abscess may develop (2).

As a foreign body, nasal packing has a number of disadvantages such as prophylactic antibiotic use, nasal pain and discomfort, edema, insufficient nasal breathing that leads to mouth breathing and dry mouth, increased lacrimation, difficulty in sleeping and cardiopulmonary complications (2-4). Various absorbable materials, tissue adhesives or suture techniques have been used to overcome the disadvantages of removable nasal packing (1,5,6).

Fibrin glue (FIB), n-butyl cyanoacrylate (NBC) and 2-octyl cyanoacrylate (2OC) are commonly used tissue adhesives. These adhesives are not only hemostatic, but also possess bacteriostatic properties (4,7,8), so they may eliminate the need for nasal packs. The ear cartilages of

Address for Correspondence: Deniz Hanci, University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital, Clinic of Otorhinolaryngology, Istanbul, Turkey
Phone: +90 532 373 28 66 E-mail: dhanci007@hotmail.com ORCID: orcid.org/0000-0002-6644-5059
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rabbits are very much alike the septal cartilage, therefore, we found it appropriate to carry out this study in a rabbit model.

In this study, we aimed to investigate the efficacy of FIB, 2OC, and NBC on the healing processes of cartilages in a rabbit model. Those three tissue adhesives are also compared to each other both clinically and histopathologically.

Methods

All experiments were performed at the Animal Research Laboratory of İstanbul Bagcilar Training and Research Hospital between March and May 2016 with the approval of the Animal Experiments Ethics Committee of İstanbul Bagcilar Training and Research Hospital (date: 23.03.2015, no: 2015/30). Experiments were conducted in accordance with the principles of the Helsinki Declaration on laboratory animals. Due to the ethical regulations of the animal ethical committee, a routine reduction in the number of experimental animals was enforced, and a total number of 10 New Zealand rabbits were provided.

Study Design

Four different groups were formed; one was the control group and the other three groups were designed as the study groups for study defined as, FIB, 2OC, and NBC groups.

Experimental Animal Model

Both ears of all rabbits were used, and for each ear, four separate incisions were made. Four flaps in the subperichondrial plane were raised delicately for each ear (Figure 1). In the control group, perichondrial flap was laid in its place without using any material between the cartilage and perichondrium. In the FIB group, FIB was placed between the cartilage and perichondrium. In the 2OC group, 2OC was placed between the cartilage and perichondrium. In the NBC group, NBC was placed between the cartilage and perichondrium. All flaps in the FIB, NBC and 2OC groups were retained to their original positions and the incision sites were pressed against the ear for 20 seconds. All incisions were then sutured.

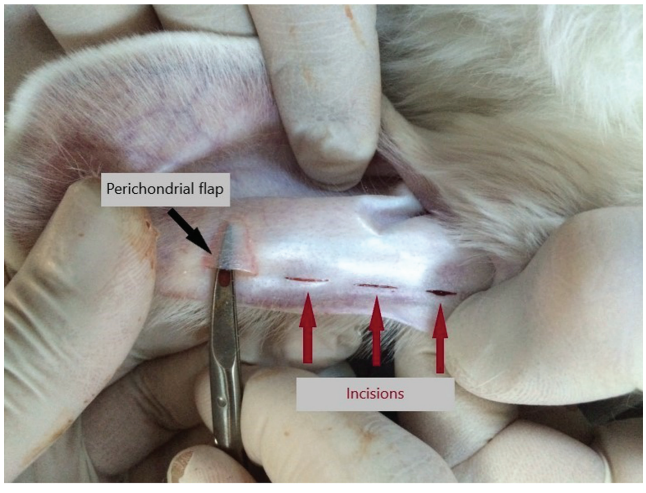

Figure 1. Separate incisions were performed and four flaps were raised in the subperichondrial plane for each ear

The right ears were examined on the 15th day and the left ears on the 30th day; samples were removed with solid tissue around the edges, treated with formol, and prepared for histological examination.

Histopathological Examination

The relevant areas of rabbit ears were isolated and incubated for 72 hours at room temperature in 10% buffered neutral formaldehyde. Histological examinations were performed on a tissue monitoring device (Leica TP 1020). After routine tissue monitoring, tissue blocks were implanted in paraffin. Sections of 5 µm thickness were stained with haematoxylin eosin. A light microscope (Leica 6000B) and a LASX program attached to a digital camera (Leica DC490, Wetzlar-Germany) were used for histological examinations. Each sample was scored and semi-quantitatively assessed for epithelial integrity and renaturation, edema, vascularity, and inflammation (0=no, 1=mild, 2=moderate, 3=severe, and 4=very severe). Epithelium and perichondrium thickness (µm) were measured with a 10-magnification image analysis program (Leica Application Suite software, Leica) and the mean values for the groups were determined.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows version 10.0. The Mann-Whitney U and Kruskal-Wallis tests were used to compare quantitative data. The chi-square and Fisher's Exact tests were used to compare qualitative data. Data were expressed as the mean ± standard deviation of the mean. A value of $p<0.05$ was considered as statistically significant.

Results

In all groups, a multi-layered flat epithelium was observed. Epithelial integrity was preserved in all groups with re-epithelization. Slight edema was observed in connective tissue under the epithelium in all groups on 15th and 30th days (Table 1).

The epithelium and perichondrium thicknesses were compared on the 15th day and were found thicker in NBC and 2OC. 2OC epithelial thickness was nearly two-fold compared to the control. Thirty-day samples exhibited decreased thickening of the epithelium in NBC and 2OC whereas the thickness of the perichondrium was increased. In FIB, epithelium thickness and perichondrial thickness did not change after 30 days (Table 2).

Table 1. Histopathological scores of the study groups

		Re-epithelialization	Edema	Inflammation	Vascularisation
15th day	Control	**3**	**1**	**2**	1
	FIB	4	1	2	2
	2OC	3	1	2	2
	NBC	3	1	1	1
		Re-epithelialization	Oedema	Inflammation	Vascularisation
30th day	Control	4	1	2	2
	FIB	4	1	2	2
	2OC	4	1	2	2
	NBC	3	1	1	1

Each sample belonging to each group has epithelial integrity and regeneration, edema, vascularization, inflammation in the range of 0-4; 0=none, 1=mild, 2=moderate, 3=severe and 4=very severe. The data reflect the mean scores of the groups. FIB: Fibrin glue, 2OC: 2-Octyl cyanoacrylate, NBC: N-Butyl cyanoacrylate

Table 2. Comparison of epithelium and perichondrium thickness in the 15th and 30th days

	15th Day		30th Day	
Groups	**Epithelium thickness**	**Perichondrium thickness**	**Epithelium thickness**	**Perichondrium thickness**
Control	368.106±6.407	55.943±1.111	489.133±6.487	49.090±0.886
FIB	327.113 ±3.138	68.593±1.377	524.514±6.677	68.600±1.758
2OC	384.893±5.455	82.776±1.941	426.680±5.399	73.413±1.573
NBC	576.073±11.794	118.553±2.069	340.093±5.450	138.706±2.036

Epithelium and perichondrium thickness measurements were made in µm in three sections of each sample and given as mean + SEM for the groups. FIB: Fibrin glue; 2OC: 2-Octyl cyanoacrylate; NBC: N-Butyl cyanoacrylate

Moderate vascularity was observed in 15-day samples from the groups treated with 2OC and FIB. Vein occlusion was observed in 15-day samples in the control and NBC groups. Moderate inflammation was observed in all 15-day samples. In NBC, thicker collagen fibrils were observed in connective tissue.

Mild inflammation was observed in all test groups except the NBC on the 30th day, but NBC had moderate inflammation. Inflammation in the control group was similar to FIB and 2OC but less in NBC.

On the 15th day, samples from 2OC and FIB exhibited a larger number of chondroblasts. Extracellular matrix synthesis was apparent in 2OC and the basophilic area around the cells was similar to the extracellular matrix in the hyaline cartilage.

On the 30th day, a round-cytoplasmic chondrocyte embedded in lacunae, a basophilic extracellular matrix in the periphery, and a cartilaginous tissue composed of flattened outer chondroblasts were observed in the control group. On the 15th day, immature cartilaginous tissue was observed in FIB; chondrocytes forming isogen groups and more chondroblasts were observed in NBC; and chondrocytes, mitochondrial chondrocytes, and chondroblast cells were observed in the group treated with 2OC.

Discussion

Nasal packing after septoplasty is still used worldwide. Although the need for nasal packing remains a matter of debate, many surgeons prefer to use it. It's used to reattach mucoperichondrial flaps onto septal cartilage, to prevent epistaxis and septal hematoma. However, nasal packing has a number of disadvantages such as nasal pain, edema, prophylactic antibiotic use, mouth breathing, dry mouth and these effects decrease the quality of life (2,4). Various absorbable materials have been used to overcome the pain during the removal of the packing. Absorbable materials do not require subsequent removal, providing the patient with increased comfort while achieving positive effects on haemostasis.

A lack of packing may have advantages such as increased comfort, decreased chance of postoperative complications associated with packing, lowered costs. A few alternative techniques to nasal packing have been described in the literature. The most commonly used technique is suturing the septum (9,10). Korkut et al. (11) compared trans-septal suturing and intranasal packing after septoplasty. Postoperative symptoms were less in the transseptal suturing group, patients were more comfortable. However, the mean duration of surgery was higher in the suture group. Gunaydin et al. (12) compared transseptal suturing and nasal packing. They suggested

that trans-septal suturing is more comfortable and cost-effective, but also they reported that postoperative discomfort due to foreign body sensation was seen in transseptal cases. Tami et al. (13) used bioresorbable septal stapler in 24 subjects, complete coaptation of the mucoperichondrial flaps was achieved in all of the patients and septal hematoma did not occur in any patient.

Habesoglu et al. (2) used FIB to fix the mucoperichondrial flap to the septal cartilage and compared outcomes with non-absorbable nasal packing. They found that pain scores in the FIB group were significantly lower than in the intranasal packing group. The postoperative bleeding was also lower in the FIB group. Erkan et al. (14) investigated the changes in rabbit nasal septal tissues after using FIB in septoplasty. They found that the use of FIB caused mucosal inflammation, increased mucosal thickness, decreased perichondrial and cartilaginous thickness and created mucosal damage. Coey et al. (15) compared the use of fibrin tissue adhesive and nasal packing in endoscopic nasal surgery in their meta-analysis and their results showed that fibrin tissue adhesive had minor advantages against nasal packing.

NBC and 2OC are bacteriostatic, hemostatic, biodegradable and tissue-compatible powerful tissue adhesives (8,16). Cyanoacrylate fixatives were approved by the Food and Drug Administration (FDA) to facilitate skin closure, but in recent years they have been used in different areas of medicine. Üstün et al. (17) repaired the incisions made on the tongues of rats with 2OC or Vicryl sutures. In their short and long-term results, they claimed that 2OC is a good alternative to primary suturing in mucosa lacerations. Alkan et al. (16) fixed the nasal septum to the anterior nasal spine in rabbits using NBC and they did not observe any kind of foreign body reaction, histotoxicity, cartilage necrosis or inflammation. Dabb et al. (18) used 2OC for the fixation of nasal cartilage grafts and reported that using 2OC was an effective method for prefabrication and fixation of nasal cartilage grafts. Brown et al. (19) reported in their short-term animal study that the stabilization of cartilage to bone with 2OC was better than the suturing technique.

In our study, we found that the epithelium and perichondrium were thicker in NBC and 2OC. In FIB, epithelium and perichondrium thicknesses were the same after 30 days. Moderate vascularity was observed in all groups, pointing out to stable cartilage viability. The number of chondroblasts were increased in all groups, suggesting that these three materials are compatible for use with cartilage as a packing material.

The ear cartilage of the rabbits is very much alike the human septal cartilage. In need of search for different materials to be used as nasal packing after septoplasty, we aimed to compare previously mentioned three chemical adhesives to a control group and examined and compared the effects and potential biohazards of them to tissues histopathologically.

Study Limitations

Our study had one limitation: due to legal and ethical regulations, the number of rabbits provided according to the ethical committee directives were less in number to conclude a concrete result, nevertheless the data we collected deemed a success in the favour of chemical adhesives.

Conclusion

Application of NBC, FIB, and 2OC between septal cartilage and perichondrium are potential alternatives to nasal packing after septoplasty. These materials have an acceptable histopathological profile in animals, based on post-operative inflammation levels, vascularisation, and the cellular characteristics of bone and cartilage regrowth. Studies can be conducted in which these adhesives are used in septoplasty surgeries in humans.

Authorship Contributions

Concept: D.H., H.A., O.U., D.Z.,B.G., Y.U., Design: D.H., H.A., O.U., D.Z.,B.G., Y.U., Data Collection or Processing: D.H., H.A., O.U., D.Z.,B.G., Y.U., Analysis or Interpretation: D.H., H.A., O.U., D.Z.,B.G., Y.U., Literature Search: D.H., H.A., O.U., D.Z.,B.G., Y.U., Writing: D.H., H.A., O.U., D.Z.,B.G., Y.U.,

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References

1. Genç E, Ergin NT, Bilezikçi B. Comparison of suture and nasal packing in rabbit noses. Laryngoscope 2004;114:639-45.
2. Habesoglu TE, Kulekci S, Habesoglu M et al. Comparative outcomes of using fibrin glue in septoplasty and its effect on mucociliary activity. Otolaryngol Head Neck Surg 2010;142:394-9.
3. Muluk NB, Apan A, Ozcakir S, Arikan OK, Koç C. Risk of respiratory distress in the patients who were applied nasal packing at the end of nasal surgery. Auris Nasus Larynx 2008;35:521-6.
4. Aksoy F, Yilmaz F, Yildirim YS, Gideroglu K, Tatar Z. Use of N-butyl cyanoacrylate in nasal septoplasty: histopathological evaluation using rabbit nasal septum model. J Laryngol Otol 2010;124:753-8.
5. Lemmens W, Lemkens P. Septal suturing following nasal septoplasty, a valid alternative for nasal packing? Acta Otorhinolaryngol Belg 2001;55:215-21.

6. Reiter D, Alford E, Jabourian Z. Alternatives to packing in septorhinoplasty. Arch Otolaryngol Head Neck Surg 1989;115:1203-5.
7. Vaiman M, Eviatar E, Segal S. The use of fibrin glue as hemostatic in endonasal operations: a prospective, randomized study. Rhinology 2002;40:185-8.
8. Min JY, Jang YJ. Use of 2-octylcyanoacrylate (Dermabond) tissue adhesive for tip graft fixation in open rhinoplasty. Otolaryngol Head Neck Surg 2011;145:737-41.
9. Bajaj Y, Kanatas AN, Carr S, Sethi N, Kelly G. Is nasal packing really required after septoplasty? Int J Clin Pract 2009;63:757-9.
10. Wang D, Liu T, Liao C, Tang G, Tian T, Tian L. Is nasal septal suturing an alternative technique to nasal packing?: A protocol for systematic review and meta-analysis. Medicine (Baltimore) 2020;99:23535.
11. Korkut AY, Teker AM, Eren SB, Gedikli O, Askiner O. A randomised prospective trial of trans-septal suturing using a novel device versus nasal packing for septoplasty. Rhinology 2010;48:179-82.
12. Günaydın RÖ, Aygenc E, Karakullukcu S, Fidan F, Celikkanat S. Nasal packing and transseptal suturing techniques: surgical and anaesthetic perspectives. Eur Arch Otorhinolaryngol 2011;268:1151-6.
13. Tami TA, Kuppersmith RB, Atkins J. A clinical evaluation of bioresorbable staples for mucoperichondrial flap coaptation in septoplasty. Am J Rhinol Allergy 2010;24:137-9.
14. Erkan AN, Cakmak O, Kocer NE, Yilmaz I. Effects of fibrin glue on nasal septal tissues. Laryngoscope 200;117:491-6.
15. Coey JG, Whittaker PJ, Williams G, Ikram UH, Page OJR. Fibrin tissue adhesive versus nasal packing in endoscopic nasal surgery: a systematic review and meta-analysis. Rhinology 2019;57:21-31.
16. Alkan S, Dadaş B, Celik D, Coskun BU, Yilmaz F, Başak T. The efficacy of N-2-butyl cyanoacrylate in the fixation of nasal septum to the anterior nasal spine in rabbits: experimental study. Eur Arch Otorhinolaryngol 2007;264:1425-30.
17. Üstün O, Kumral TL, Atar Y, et al. Histopathological Comparison of 2-Octyl Cyanoacrylate and Primary Suturing for Tongue Lacerations. J Craniofac Surg 2020;31:e334-e7.
18. Dabb RW, Gaffield JW, Camp LA. Use of cyanoacrylate (super glue) for the fixation and prefabrication of nasal cartilage grafts. Aesthet Surg J 2001;21:328-33.
19. Brown PN, McGuff HS, Noorily AD. Comparison of N-octyl-cyanoacrylate vs suture in the stabilization of cartilage grafts. Arch Otolaryngol Head Neck Surg 1996;122:873-7.