

Use of N-butyl cyanoacrylate in nasal septoplasty: histopathological evaluation using rabbit nasal septum model

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Abstract

Objectives: This study was designed to investigate the effects of the tissue adhesive N-butyl cyanoacrylate on nasal septal tissues after septal surgery in a rabbit model.

Methods: Forty-two adult New Zealand rabbits were randomly divided into three groups (14 in each group): septoplasty alone, septoplasty plus N-butyl cyanoacrylate, and controls. The open approach was used to explore the nasal septum. After raising mucoperichondrial and mucoperiosteal flaps on both sides of the septum, the septum was detached from the nasal floor in the septoplasty alone and septoplasty plus N-butyl cyanoacrylate groups. In the septoplasty plus N-butyl cyanoacrylate group, the mucoperichondrial and mucoperiosteal flaps were fixed to the septum and the septum was fixed lateral to the nasal spine using N-butyl cyanoacrylate; in the septoplasty alone group, the septum was packed with Merocel. In the control group, no further septal surgery was performed after flap elevation. Animals were observed for bleeding and haematoma formation over the first 24 hours. Seven animals in each group were used to evaluate early histopathological effects on the septal tissues, at four weeks post-operatively; the other seven in each group were used to evaluate late effects, at 12 weeks.

Results: Haematoma formation was observed in 10 animals in the septoplasty alone group, in four animals in the control group, and in only one animal in the septoplasty plus N-butyl cyanoacrylate group. The difference in haematoma incidence between the septoplasty alone and the septoplasty plus N-butyl cyanoacrylate groups was significant ($p = 0.000$). Histopathological evaluation revealed no significant difference between the groups as regards granulation tissue formation at week four versus week 12; however, there was a significant difference between the septoplasty plus N-butyl cyanoacrylate group and the control groups as regards inflammation at week 12 ($p = 0.038$). There was a significant difference between the septoplasty plus N-butyl cyanoacrylate group and the septoplasty alone group as regards the composition of the bone–cartilage junction zone at week four ($p = 0.001$). There was also a significant difference between the septoplasty plus N-butyl cyanoacrylate group and the control group as regards the cellular structure of new cartilage formation at week 12 ($p = 0.004$).

Conclusions: In this rabbit septoplasty model, N-butyl cyanoacrylate appeared to be an effective nasal tissue adhesive, with a low complication rate.

Key words: Nasal Septum; Septoplasty; Wound Healing; Tissue Adhesive; Cyanoacrylate

Introduction

Septoplasty has for decades been the preferred surgical technique for managing nasal septal deviation with obstruction of nasal airflow.¹ Following septal surgery, nasal packing is undertaken with the aim of stabilising the healing septum and preventing septal haematoma; however, this is not an innocuous procedure.² The most common problem encountered by patients after septoplasty is pain and discomfort during removal of nasal packs.³ Moreover,

cardiovascular changes,⁴ obstructive sleep apnoea⁵ and toxic shock syndrome⁶ are among the possible complications associated with this procedure. In addition to the mucosal bleeding risk during removal of packing, the placement and removal procedures themselves may cause nasal trauma.⁷ However, omission of nasal packing, due to related complications such as pain, is associated with a greater risk of other adverse events, such as unstable blood pressure due to post-operative pain, and

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infiltration of blood into the oropharynx and nasopharynx (due to inhibition of the cough reflex by local anaesthetics) and aspiration.⁸ Thus, alternatives to nasal packing are highly desirable.

N-butyl cyanoacrylate is a powerful tissue adhesive which is bacteriostatic, biodegradable and tissue-compatible.^{3,7,8} It has been used to achieve haemostasis, embolisation, obliteration, retinal tear repair, corneal ulcer treatment, fixation of osteotomies and facial fractures, skin laceration repair, and cartilage graft fixation, amongst other applications.^{9–13} The use of N-butyl cyanoacrylate to fix the caudal edge of the septum to the anterior nasal spine may reduce the need for post-operative tamponade following nasal septal surgery; it may also reduce the risk of post-operative haemorrhage, by means of a sclerosing effect of the tissue, and provide more efficient septum stabilisation than tamponade.

Therefore, the present study was designed to investigate the utility of N-butyl cyanoacrylate in nasal septoplasty surgery, in a rabbit model, with respect to stabilisation of the nasal septum and prevention of haematoma formation, as assessed by histopathological analysis.

Materials and methods

Animals

A total of 42 adult New Zealand rabbits of both sexes, weighing 2.5–3.0 kg, were kept in a light- and temperature-controlled room with cycles of 12 h light and 12 h dark, with constant temperature ($22 \pm 0.5^\circ\text{C}$) and relative humidity (65–70 per cent).

N-butyl cyanoacrylate (Histoacryl[®]; B Braun Malsungen AG, Malsungen, Germany) was used as the tissue adhesive. All experiments were performed at the Animal Research Laboratory of the Istanbul University Cerrahpasa Faculty of Medicine. Experiments were conducted in accordance with the principles of the Helsinki Declaration on the use of laboratory animals.

The animals were divided into three groups: septoplasty alone, septoplasty plus N-butyl cyanoacrylate, and controls. Each group comprised 14 animals. In order to evaluate the effect of N-butyl cyanoacrylate in the early and late post-operative phases, half of the animals ($n = 7$) in each group were sacrificed at week four post-operatively (i.e. early phase) and the other half at week 12 (i.e. late phase).

Surgical procedure

The septoplasty technique has been described by Alkan *et al.*¹³ Acepromazine maleate (0.5 mg/kg) and ketamine hydrochloride (25–30 mg/kg) were used intramuscularly for anaesthesia. The surgical field was prepared by washing with povidone-iodine and draping. The procedure was carried out under loupe magnification (2.5×340 mm loupe; Heine HR, Henleys Medical Supplies Ltd. Welwyn Garden, Hertfordshire, UK) to improve surgical vision. Two millilitres of 1 per cent lidocaine hydrochloride with 1:200 000 adrenaline was injected into the columellar region and the submucoperichondrial

plane, on both sides of the septum. The septum was approached by the open technique, using a transcollellar incision. After the incision, the caudal aspect of the septum was exposed. Using a Freer elevator, bilateral mucoperichondrial flaps were elevated posteriorly to the junction of the bone and cartilage. Following flap elevation, in the septoplasty alone and septoplasty plus N-butyl cyanoacrylate groups, the septum was completely freed with number 11 surgical blades by detachment from the ethmoid lamina perpendicularis and vomer posteriorly and from the maxillary bone inferiorly. In the control group, mucoperichondrial flaps were elevated but the septum was left intact.

In the septoplasty plus N-butyl cyanoacrylate group, the mucoperichondrial flaps were reattached to the septum using N-butyl cyanoacrylate. In the septoplasty alone group, the septum was packed with Meroceol (Meroceol[®]; Medtronic ENT, Jacksonville, Florida, US). In the control group, the mucoperichondrial flaps were shifted to the same point and left to heal by secondary intention, using no fixation method. The columellar incision was closed primarily with 4/0 chromic catgut suture. All operations were performed by the same surgeon.

During the first 24 hours post-operatively, all animals were observed for bleeding and septal haematoma formation. The septum was evaluated macroscopically for perforation in all animals at weeks four and 12, prior to sacrifice and histopathological evaluation.

After sacrifice by decapitation, the animals' septa were evaluated. In the septoplasty plus N-butyl cyanoacrylate group, tissue samples were taken from the N-butyl cyanoacrylate application area and preserved in 10 per cent formaldehyde solution for histopathological examination. Sections of 4–6- μm thickness were cut, stained with haematoxylin and eosin, and examined under a light microscope by the same, blinded pathologist. Changes relating to inflammation, foreign body reaction and histotoxicity

TABLE I

CRITERIA FOR HISTOPATHOLOGICAL EVALUATION OF SEPTUM

Parameter	Score & meaning
Foreign body reaction	0 = no 1 = yes
Level of inflammation	0 = none 1 = mild 2 = moderate 3 = extensive 4 = extensive + tissue necrosis
Granulation tissue	0 = no 1 = yes
Bone–cartilage junction zone	0 = fibrotic 1 = fibrocartilaginous 2 = cartilaginous 3 = bony
Cellular structure of new cartilage	0 = normal or proliferation 1 = empty lacune foci 2 = empty lacune segment & hypocellularity 3 = diffuse hypocellularity 4 = no living cells

TABLE II
RESULTS FOR HAEMATOMA AND SEPTAL PERFORATION

Group	Haematoma? (at week four)		Septal perforation? (at week 12)	
	Yes	No	Yes	No
Septoplasty + B2-CA*	1	13 [†]	1	13
Septoplasty alone*	10	4	0	14
Control*	4	10	0	14

*n = 14. [†]p = 0.000 vs septoplasty alone. B2-CA = N-butyl cyanoacrylate

were evaluated, using the classification criteria previously described by Alkan *et al.* (Table I).¹³

Statistical analysis

The Statistical Package for the Social Sciences for Windows version 10.0 software was used for analysis and evaluation of data. The Kruskal–Wallis and Mann–Whitney U tests were used to compare quantitative data. The Fisher’s exact and chi-square tests were used to compare qualitative data. Data were expressed as the mean ± the standard error of the mean. A value of p < 0.05 was considered statistically significant.

Results

Macroscopic evaluation

Septal haematoma. A septal haematoma was observed in 10 animals in the septoplasty alone group, four in the control group, and only one in the septoplasty plus N-butyl cyanoacrylate group. A significant difference in haematoma incidence was found between the septoplasty plus N-butyl cyanoacrylate group and the septoplasty alone group (p = 0.000), but not between the septoplasty plus N-butyl cyanoacrylate group and the control group (although the haematoma incidence was high in the control group) (Table II).

Septal perforation. No septal perforation was observed in any animal at week four post-operatively. At week 12, septal perforation was observed in only one animal, in the septoplasty plus N-butyl cyanoacrylate group. No significant difference was found between the groups in this respect (Table II).

Histopathological evaluation

Upon histopathological evaluation, a foreign body reaction was observed in two animals at week four and in one animal at week 12, all within the septoplasty plus N-butyl cyanoacrylate group (Table III). No other foreign body reactions were observed.

Granulation tissue formation was observed in all animals at weeks four and 12, decreasing at week 12.

At week four, we observed mild to moderate inflammation between the mucoperichondrium and the underlying cartilage at week 12. In the septoplasty plus N-butyl cyanoacrylate group, also we observed same group with mild to moderate inflammation at week 12, while negligible inflammation was found in the other two groups at either time point. At week 12, there was an insignificant difference between the septoplasty plus N-butyl cyanoacrylate group and the septoplasty alone group as regards inflammation level, but a significant difference between the septoplasty plus N-butyl cyanoacrylate group and the control group in this respect (p = 0.038) (Table IV).

In all animals of the septoplasty alone and the septoplasty plus N-butyl cyanoacrylate groups, the bone–cartilage junction zone between the caudal edge of the septum and the maxillary bone remained fibrotic with cartilaginous growth at week four. At week four, there was a significant difference in new cartilage formation in this zone, comparing the septoplasty plus N-butyl cyanoacrylate group and the septoplasty alone group, and also comparing the septoplasty plus N-butyl cyanoacrylate group and the control group (p = 0.001 for both) (Table IV). All animals had fibrocartilaginous tissue in the bone–cartilage junction zone at week 12 (Table IV).

In the septoplasty plus N-butyl cyanoacrylate group, the newly formed cartilage cells had empty lacune cell segments and hypocellularity at both early (week four) and late (week 12) stages. In the septoplasty alone group, newly formed cartilage cells were normal or showed proliferation at week four and week 12 (Table IV). At week 12, there was a significant difference between the septoplasty plus N-butyl cyanoacrylate group and the control group as regards the cellular structure of newly formed cartilage cells (p = 0.004) (Table IV).

Discussion

N-butyl cyanoacrylate is known to be an effective tissue adhesive which is bacteriostatic, biodegradable

TABLE III
RESULTS FOR GRANULATION TISSUE FORMATION AND FOREIGN BODY REACTION

Group	Granulation tissue formation?				Foreign body reaction?			
	Week 4		Week 12		Week 4		Week 12	
	Yes	No	Yes	No	Yes	No	Yes	No
Septoplasty + B2-CA*	5	2	2	5	2	5	1	6
Septoplasty alone*	3	4	1	6	0	7	0	7
Control*	1	6	1	6	0	7	0	7

*n = 7. B2-CA = N-butyl cyanoacrylate

TABLE IV
HISTOPATHOLOGICAL CRITERIA SCORES IN THE THREE GROUPS

Parameter	Control		Septoplasty alone		Septoplasty + B2-CA	
	Week 4	Week 12	Week 4	Week 12	Week 4	Week 12
Level of inflammation	0.29 ± 0.18	0.29 ± 0.18	0.57 ± 0.20	0.42 ± 0.18	1.29 ± 0.52	1.29 ± 0.36*
Bone–cartilage junction zone	1.0 ± 1.0	1.0 ± 1.0	0.0 ± 0.0	1.0 ± 0.0	0.14 ± 0.14 [†]	0.85 ± 0.14
Cell structure of new cartilage	0.0 ± 0.0	0.0 ± 0.0	0.14 ± 0.14	0.43 ± 0.20	2.0 ± 0.44	1.29 ± 0.29 [‡]

Data represent mean ± standard error of the mean. * $p = 0.038$ vs control group; [†] $p = 0.001$ vs septoplasty alone and control groups; [‡] $p = 0.004$ vs control group. B2-CA = N-butyl cyanoacrylate

and tissue-compatible.^{14–16} Previous studies on rabbits have revealed no significant histotoxicity or cartilage necrosis, but noted mild inflammation during fixation of an autogenous maxillary bone graft onto auricular cartilage,¹⁶ and during augmentation rhinoplasty.¹⁷ N-butyl cyanoacrylate has also been shown to preserve the viability of cartilage and chondrocytes *in vitro*.¹⁸ N-butyl cyanoacrylate has been found to be effective in the fixation of the nasal septum to the anterior nasal spine in rabbits, without any foreign body reaction, histotoxicity, cartilage necrosis or inflammation.¹³ It has also been found to enable simpler, quicker autogenous cartilage fixation in external rhinoplasty patients, compared with suture, with no significant complications.¹⁹ N-butyl cyanoacrylate safely used animal rhinological operation but N-butyl cyanoacrylate not use in human septoplasty.

At week four, we observed mild to moderate inflammation between the mucoperichondrium and the underlying cartilage at week 12. In the septoplasty plus N-butyl cyanoacrylate group, also we observed same group with mild to moderate inflammation at week 12. There was a significant difference between the septoplasty plus N-butyl cyanoacrylate group and the control group as regards degree of inflammation ($p = 0.038$), but not between the septoplasty plus N-butyl cyanoacrylate group and the septoplasty alone group. The small but statistically significant increase in inflammation in the septoplasty plus N-butyl cyanoacrylate group at weeks four and 12, compared with the control group, may be related to the large amount of cyanoacrylate used, but is probably more influenced by the extent of the septal cartilage surgery (as previously stated, an insignificant difference in inflammation was observed between the septoplasty plus N-butyl cyanoacrylate group and the septoplasty alone group).

It has previously been shown in a rabbit model that fibrocartilaginous tissue develops between the transected nasal septum and the anterior nasal spine between the ninth and 12th post-operative weeks; similarly, in the current study we observed that the fibrous tissue observed between the two cartilages at week four had become fibrocartilaginous by week 12.¹³ Our findings indicate that the septoplasty procedure induces the development of a fibrocartilaginous junction zone between the bone and the cartilage tissue, regardless of whether N-butyl cyanoacrylate is used or not. The most prominent influence of N-butyl cyanoacrylate seems to be on the character of the newly formed cells in this

zone. Our study showed that usage of N-butyl cyanoacrylate resulted in hypocellularity and empty lacune segments in newly formed cartilage tissue, at both week four and week 12. However, the difference in the cellular structure of new cartilage, comparing septoplasty plus N-butyl cyanoacrylate versus control groups, was significant only at week 12, being insignificant at week four. Accordingly we may suggest that in early period of surgery may have minimal negative effect on cartilage cells and by the time this negative effect reduces. In our opinion, the hypocellularity and empty lacune segments observed at week 12 in the septoplasty alone group and the septoplasty plus N-butyl cyanoacrylate group were mostly related to the septal cartilage surgery undertaken.

We observed septal perforation ($n = 1$), foreign body reaction ($n = 1$) and granulation tissue formation ($n = 2$) in the septoplasty plus N-butyl cyanoacrylate group at week 12 (Figures 1 and 2). However, these observations did not differ significantly from the control group, and our findings were similar to previously published results.

Septoplasty is a frequently performed procedure. The most common post-operative problem is pain and discomfort during removal of nasal packing. Such packs are commonly used to prevent post-operative epistaxis²⁰ and septal haematoma,² and to stabilise the healing septum. The removal of nasal

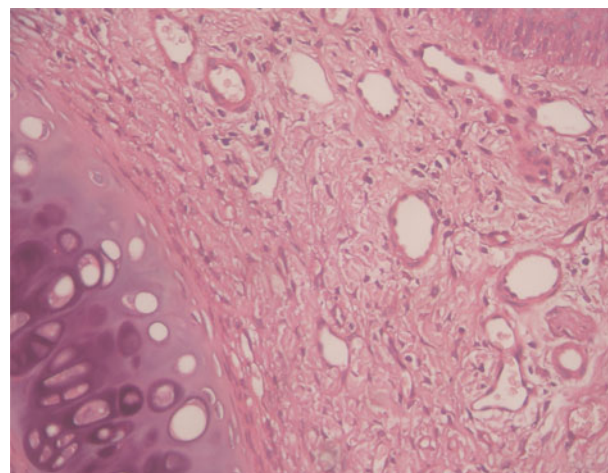


FIG. 1

Photomicrograph of tissue sample obtained at week four from an animal from the septoplasty plus N-butyl cyanoacrylate group, showing granulation tissue. (H&E; ×400)

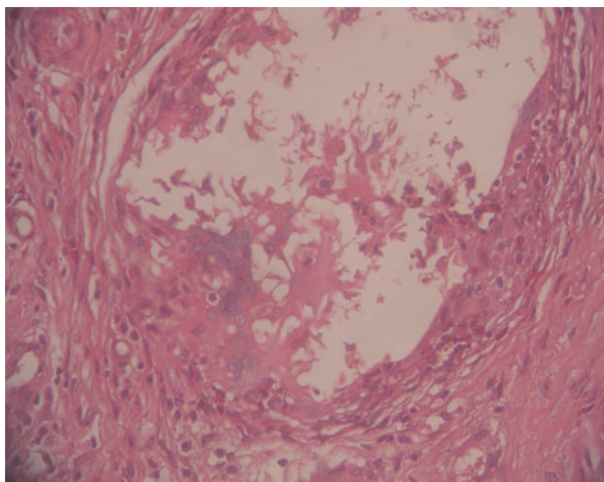


FIG. 2

Photomicrograph of tissue obtained at week 12 from an animal from the septoplasty plus N-butyl cyanoacrylate group, showing foreign body reaction. (H&E; $\times 400$)

packs is quick²¹ but may be associated with severe pain, and various studies have investigated how to make the procedure less painful.²² Some methods are difficult and relatively impractical, including wrapping the packs with Gelfilm or Meroce1,²³ blocking the sphenopalatine ganglion,²⁴ hydrating packs with topical local anaesthetic,²⁵ and keeping packs inside the nose for shorter periods of time.²⁶

- **This study was designed to investigate the effects of the tissue adhesive N-butyl cyanoacrylate on nasal septal tissues after septal surgery in a rabbit model**
- **N-butyl cyanoacrylate may be a good alternative to nasal packing, due to its haemostatic and tissue adhesive properties observed in rabbits**
- **It has an acceptable histopathological profile in these animals, as assessed from post-operative inflammation levels, granulation tissue formation, foreign body reaction, and the cellular characteristics of bone and cartilage regrowth; it also has a low complication rate**
- **These findings should be supported by further studies assessing its utility in septoplasty in humans**

The tissue adhesive N-butyl cyanoacrylate may offer an effective alternative to nasal packing, currently still an integral part of nasal surgery. Our data indicated that, in a rabbit model, the use of N-butyl cyanoacrylate helped prevent bleeding and septal haematoma formation in the early post-operative period, presumably due to the compound's haemostatic properties. N-butyl cyanoacrylate also fixed the mucoperichondrial flaps to the septum and the septum to the maxillary bone (two basic

goals of nasal packing). These data are supported by the findings of other, recent studies.^{9–15} The use of N-butyl cyanoacrylate may obviate the need for nasal packs, sparing patients the pain of their removal.³ It may also enable the complications of nasal packing to be avoided, such as cardiovascular changes,⁴ obstructive sleep apnoea⁵ and toxic shock syndrome.⁶ N-butyl cyanoacrylate may have other potential advantages for patients (including the absence of post-operative nasal obstruction, and an earlier return to work) and for surgeons (including shorter duration of surgery and avoidance of post-operative nasal packing problems).

Overall, our own findings and those of others indicate that N-butyl cyanoacrylate is bacteriostatic, biodegradable, tissue-compatible and without significant complications; it may also be quicker and simpler to use for septoplasty, enable reduced operating time, and be more comfortable, compared with nasal packing.

The benefits of N-butyl cyanoacrylate have been clearly demonstrated in rabbit septoplasty models; however, its application for routine septoplasty in humans is as yet unknown.

The recent development of a nasal septal stapling device offers another new alternative to nasal packing after septoplasty.^{27,28}

Conclusion

N-butyl cyanoacrylate would appear to have potential as a beneficial alternative to nasal packing after septoplasty, due to its haemostatic and tissue-adhesive properties observed in rabbits. It has an acceptable histopathological profile in these animals, as assessed from post-operative inflammation levels, granulation tissue formation, foreign body reaction, and the cellular characteristics of bone and cartilage regrowth; it also has a low complication rate. However, these data must be supported by further studies assessing the utility of N-butyl cyanoacrylate in septoplasty in humans.

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