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Original Article

What is the effect of Bioglue® tissue adhesive on saphenous vein graft endothelium exposed to high pressure? An experimental model

Bioglue® doku yapıştırıcısının yüksek basınca maruz kalan safen ven greft endoteline etkisi nedir? Deneysel bir model

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ABSTRACT

Objective: This study aims to investigate the effect of BioGlue (BG) in preventing cellular damage due to pressure increase in saphenous vein grafts (SVGs) used in coronary artery surgery.
Method: Twenty volunteers were accepted into this ex vivo study. SVGs were kept in circulation in the cardiopulmonary bypass (CPB) machine for 60 minutes at a pressure of 120 mmHg and a flow rate of 250 ml/min.
Results: In the BG treatment group; Type 1 endothelial damage was observed in five samples (25%), Type 2 endothelial damage in nine samples (45%), and Type 3 endothelial damage in two samples (10%). No endothelial damage was observed in 4 samples.
Conclusion: It was observed that the application of BG on the saphenous vein graft under high pressure did not cause endothelial damage due to tissue stiffness that developed.

Keywords: Coronary artery disease, endothelial damage, saphenous vein graft

ÖZ

Amaç: Bu çalışmanın amacı koroner arter cerrahisinde kullanılan safen ven greftlerinde (SVG) BioGlue'nun (BG) basınç artışına bağlı hücresel hasarı önlemedeki etkisini araştırmaktır.
Yöntem: Bu ex vivo çalışmaya yirmi gönüllü kabul edildi. SVG'ler, 120 mmHg basınçta, 250 ml/dk akış hızında kardiyopulmoner bypass (CPB) makinesinde 60 dakika sirkülasyonda tutuldu.
Bulgular: BG tedavi grubunda; beş örnekte (%25) Tip 1 endotel hasarı, dokuz örnekte (%45) Tip 2 endotel hasarı ve iki örnekte (%10) Tip 3 endotel hasarı gözlendi. Dört örnekte endotel hasarı gözlenmedi.
Sonuç: Safen ven greftine yüksek basınç altında BG uygulamasının gelişen doku sertliği nedeniyle endotel hasarına neden olmadığı gözlendi.

Anahtar kelimeler: Koroner arter hastalığı, safen ven grefti, endotel hasarı

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INTRODUCTION

The aim of coronary artery bypass graft (CABG) is to increase the quality and duration of life. Therefore, it is important that the grafts used have a high patency rate. It is known that the patency of saphenous vein grafts (SVGs) is shorter compared to arterial grafts. Many factors affect patency rates in SVGs. Among these, the surgical techniques used are as important as the risk factors of the patient.

In one study, the angiographic patency rates of both arterial and venous coronary grafts were 95.7%, 90.1%, and 92.2% in the early period, first year, and fifth year, respectively. SVGs angiographic patency rates were found to be 93.1%, 85.6%, and 91.3%, respectively (1).

Thromboembolic events in the saphenous vein due to early endothelial damage may cause graft occlusion (2). Therefore, minimizing SVG damage will significantly increase the quality of life and duration of patients. After CABG operation, tension-related endothelial damage occurs in the SVG wall exposed to arterial pressure. The inflammatory process begins secondary to this developing damage. Uncontrolled proliferation and cell migration in endothelial cells, hyperplasia in vascular smooth muscle cells, and myofibroblast formation result in neointimal hyperplasia (3,4). Therefore, SVG occlusion may develop in the early period. In order to prevent endothelial damage secondary to high arterial pressure, there are many studies in the literature on perivenous support treatments, tissue adhesives, and medical treatments (5-7).

This study aims to show the effect of hardening that occurs when BioGlue (BG) is applied to the tissue on SVG endothelium under high pressure.

MATERIALS AND METHODS

This ex vivo study was initiated after the local ethics committee's approval (Ethics Committee Date: 16/06/2021 No: 2021-11/4). Our experiment was performed on SVG taken from patients who underwent coronary artery surgery in a cardiovascular surgery clinic. Twenty patients were included in our study. For the experiment, two saphenous veins with an average length of 3 cm were prepared from each patient. The materials were divided into two groups. The first group is the treatment group, and BG was applied to the outer surface of the saphenous vein by squeezing. The second group was called the control group and the saphenous vein was used without any treatment. A total of 40 test samples were examined.

Pine-tipped cannulas were connected to both ends of the SVGs. The stoppers on the venous line side of the pine-tipped cannulas inserted into the saphenous vein were removed. Thus, the obstructing pressure factors in the flow direction were removed. An arterial system model was created using a cardiopulmonary bypass (CPB) machine by connecting an arterial line to one end of the saphenous vein and a venous line to the other end (Figure 1). A manometer was connected to the venous line to measure the pressure of the saphenous vein. BioGlue® (CryoLife Inc., Kennesaw, GA) was sprayed onto the exterior of one of the SVGs and allowed to dry for 3 minutes. This material was included in the treatment group. The other SVG did not receive any treatment and was included in the control group. This arterial system model was exposed to blood flow for 60 minutes at an average pressure of 120 mmHg and a flow rate of 250 ml/min using a CBP machine. In the experiment, the patient's own blood was used in the CPB machine. At the end of the experiment, the materials were sent to the laboratory for histopathological examination.

In this experimental study, patients who underwent off-pump surgery, underwent emergency surgery, had insufficient saphenous vein graft, had hematologic or oncologic comorbidities, and were not volunteers were excluded.

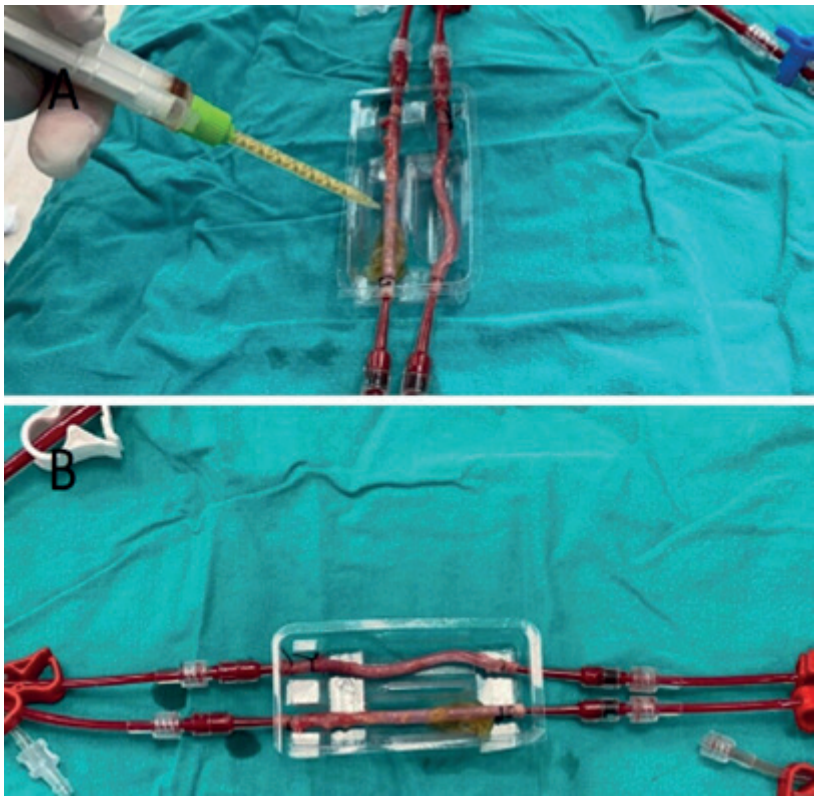

Figure 1. A: Perivascularly applied BG for external support to one of the saphenous vein grafts prepared from the same patient. B: Establishment of the experimental setup and creation of the artery model using the CPB machine.

Histopathological examination

The extracted SVGs were stored for 24 hours in a 10% buffered formaldehyde solution. Preparations stained with hematoxylin-eosin (H&E) were examined and the preparations that best represented vessel morphology were selected. In the immunohistochemical study, endothelial markers CD31 (clone EP78) rabbit monoclonal antibody Cell Marque and CD34 (clone QBend-10) mouse monoclonal antibody Cell Marque dyes were used. Immunohistochemical staining was performed with an automatic stainer (Ventana BenchMark Ultra).

The histomorphological classification of endothelial damage was made according to the classification made by Ip et al. as follows (8).

No damage: All endothelial cells are interconnected. There is no change in cell sizes and no separation between layers.

Type 1 damage: Endothelial cell integrity is preserved and all the cells are in contact with each other, but a decrease in the diameter of the endothelial cells is observed. There are slight separations in the intima and/or media layers of the vessel.

Type 2 damage: The connections between endothelial cells are broken in places and there is a loss of endothelial cells in places. There are more distinct separations in the intima and/or media layers of the vessel (Figure 2).

Type 3 damage: The endothelial cell layer is lost. There are significant separations in the intima and/or media layer of the vessel (Figure 2).

Statistical analysis

The data are categorical and calculated using IBM SPSS Statistics v.25. The Chi-Square method was used to analyze two independent categorical data. Pearson Chi-Square method was used for

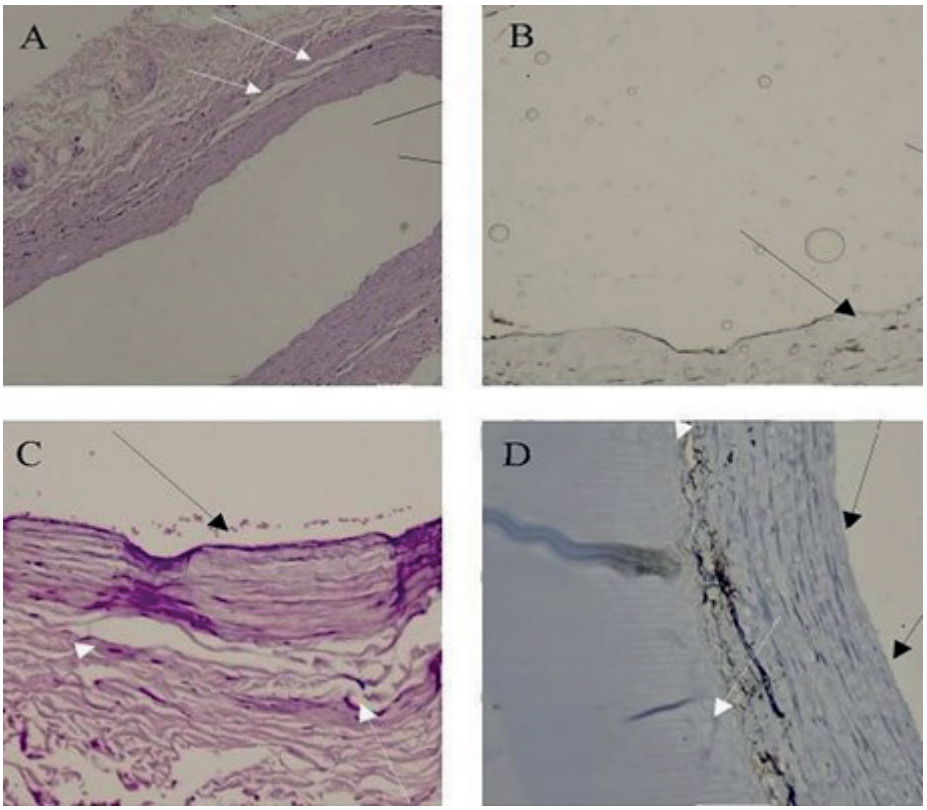

Figure 2. A: Localized loss of endothelial cells (black arrows) and separation in the intimal layer (white arrows) (H&E, x4). B: Endothelial cells marked with CD31 and areas of endothelial cell loss in between (black arrows) (CD31 IHC, x10). C: Significant loss of endothelial cells (black arrows) and marked separation of layers (white arrows) (H&E, x10). D: No labeling of the endothelium with CD31 (black arrows). Adhesive surrounding the vessel is indicated by white arrows (CD31 IHK, x10).

analysis if the expected count below 20% of the cells was less than 5 cells. Fisher's Exact Test was used when over 20% of the cells' expected count was less than 5 cells. Continuity Correction was used when the expected value over 20% of the cells was between 5-25 and Pearson Chi-Square was used when the expected value over 20% of the cells was greater than 25.

RESULTS

When endothelial damage classification is made, no significant injury was observed in four specimens (20%) in the control group, type 1 injury was detected in seven specimens (35%), type 2 injury in seven specimens (35%), and type 3 injury in two specimens (10%). In the BG treatment group, Type 1 endothelial damage was observed in five samples (25%), Type 2 endothelial damage in nine samples (45%), and Type 3 endothelial damage in two samples (10%). No endothelial damage was observed in four samples (20%) in this group.

In the control group, an increase in SVG diameter secondary to increased intraluminal pressure and endothelial damage due to severe distension occurred. There was no significant change in the saphenous vein diameter in the treatment group. Hardening was observed on the saphenous vein due to BG application. Therefore, endothelial damage secondary to intraluminal pressure is less developed. Similar endothelial damage and tunica media defects were observed in the histopathological examination of both groups. When the results are compared, a similar number of endothelial damages were observed in the treatment group and the control group (Table 1).

Table 1. Distribution of saphenous vein injury in the groups as per classification.

Vascular damage class	Group 1 (BG) (n: 20)	Group 2 (Control) (n: 20)	P value
No injury n (%)	4 (20)	4 (20)	1.000
Type 1 Endothelial damage n (%)	5 (25)	7 (35)	0.490
Type 2 Endothelial damage n (%)	9 (45)	7 (35)	0.519
Type 3 Endothelial damage n (%)	2 (10)	2 (10)	1.000

DISCUSSION

The long-term success of CABG operations is closely related to the patency rates used. Endothelial damage in venous grafts results in neointimal hyperplasia which plays an important role in morbidity and mortality by causing graft occlusion.

Multiple factors cause bleeding in heart surgery, increasing both morbidity and mortality. BioGlue® is a two-component surgical adhesive that contains 45% pure bovine serum albumin (BSA) and 10% glutaraldehyde. The two components are administered in a predetermined ratio from a double-barrel syringe and mixed within the delivery tip. The glutaraldehyde molecules covalently connect (crosslink) the BSA molecules to each other and, when applied, to the tissue proteins at the healing site, forming a mechanical closure that is independent of the coagulation cascade (9).

Perivascular application of fibrinogen glue on the saphenous vein showed a protective effect against endothelial damage secondary to high intraluminal pressure. In this study, Fibrin Glue (FG) application showed that it provided external support to the graft without any chemotactic effect and provided primary protection for the graft against endothelial damage caused by high pressure. For this reason, we believe that graft patency rates will be better thanks to the effect of preventing endothelial damage caused by the mechanical and chemical means, as well as the hemorrhage-stopping effect of FG. However, more in vivo studies are needed to investigate the effects of the graft in the long term (9). Azadani et al.[10] reported that normal physiological vascular dilatation may be limited due to the mechanical strength it creates around the BG tissue. The effect of BG on tissue support on human SVG segments is comparable to our study of cyanoacrylate, another tissue adhesive used (6). We show that the perivenous cyanoacrylate adhesive support provides external support to the graft without any chemotactic effect in SVGs and provides the vaccine's primary protection against damage from excessive stress. We achieved the same protective effect in this study.

Stoker et al. conducted a similar investigation on the saphenous vein at modest intraluminal pressures (60 mmHg) and found that providing appropriate external vein support with fibrin glue prevented severe straining and endothelial damage (11). The distinction between our study and theirs is that we showed that BG protects against alterations in SVG under 120 mmHg pressure. Table 1 summarizes the findings of our research. In 2011, the case report of Han and friends found a narrowing in the SVG secondary to the use of BG in a patient who underwent coronary bypass and reported that this narrowing developed due to the use of BG (12). In this report, we think that BG is used when there is no pressure in the saphenous vein and that stenosis is caused by the mechanical compression effect of BG. In our study, no stenosis was observed in the SVG, since we applied BG under pressure.

Ip et al.[8] divided endothelial injury into three types. Endothelial damage was defined as: type 1 injury: normal morphology despite functional changes in the endothelial layer; type 2 injury: endothelial layer detachment, local peeling, and preservation of the inner elastic lamina and medial layer despite intimal damage; type 3

damage: peeling of the endothelial layer followed by the formation of lower endothelial tissue and intimal and medial damage in the corresponding classification. They reported that especially type 3 injury may result in stenosis and occlusion in the coronary artery. Table 1 summarizes the findings of our research.

Okazaki et al.[13] classify endothelial damage in five stages.
Stage 1: normal morphology
Stage 2 and 3: minor or widespread adhesion of blood cells (corresponding to type 1 injury)
Stage 4: rarely isolated detachment of endothelial cells (corresponding to type 2 injury)
Stage 5: generalized endothelial cell deficiency (corresponding to type 3 injury)

In particular, the development of type 3 (stage 5) injury and the formation of a common lower endothelial layer will lead to platelet aggregation and thrombus formation as a result of the contact of this layer with blood components. In this circumstance, mitogens will cause smooth muscle to migrate and proliferate and as a result, the anastomotic region may experience early or late stenosis or occlusion.

Slezak et al.[14] reported widespread inflammation in the rabbit aorta of BG caused by lymphocytes, plasma cells, and eosinophilic granulocytes.

When endothelial damage was classified in our study, no significant injury was observed in four specimens in the control group, type 1 injury was detected in seven specimens, type 2 injury in seven specimens, and type 3 injury in two specimens. While endothelial damage was not observed in four samples in the treatment group, type 1 damage was observed in five samples, type 2 damage was observed in nine samples, and type 3 endothelial damage was observed in two samples. When the results are compared, we obtained statistically similar results in the control and treatment groups (Table 1). In this study, we showed that the application of BG on the perivenous SVG provides extravascular support. In addition, we have shown that BG application does not have an increasing effect on endothelial damage due to intraluminal pressure and mechanical stress. However, further research will be needed to find solutions to coronary graft failure.

CONCLUSION

BG adhesive application did not increase endothelial damage secondary to high intraluminal pressure. External vein graft support with BG may provide adequate protection against SVG damage in the early period and may support the remodeling of the vein graft according to arterial wall properties. In this way, it provides protective support against complications that may occur in the anastomosis area and on the graft. In addition to the hemostatic effect of BG, we believe that graft patency rates will be better since it does not increase endothelial damage caused by mechanical and chemical means.

LIMITATIONS OF THE STUDY

The major limitation of our study is the lack of long-term results. Another limitation is that it is done with a small number of samples.

Ethics Committee Approval: The study protocol was approved by the Bursa City Hospital Clinical Research Ethics Committee (2021-11/4 / 16.06.2021).

Conflict of Interest: The authors have declared that they have no conflict of interest.

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REFERENCES

1. Sohn SH, Kim SH, Hwang HY, Kim K-B. Mid-Term Outcomes and Angiographic Patency of Redo Coronary Artery Bypass Grafting: A Comparison between Off-Pump and On-Pump Surgery. J Chest Surg. 2021; 54(2): 106-16. https://doi.org/10.5090/jcs.20.122

2. Kouzi-Koliakos K, Kanellaki-Kyparissi M, Marinov G, et al. Prebypass histological and ultrastructural evaluation of the long saphenous vein as a predictor of early graft failure. Cardiovasc Pathol. 2006; 15(6): 336-46. https://doi.org/10.1016/j.carpath.2006.07.005
3. Sur S, Sugimoto JT, Agrawal DK. Coronary artery bypass graft: why is the saphenous vein prone to intimal hyperplasia? Can J Physiol Pharmacol. 2014; 92(7): 531-45. https://doi.org/10.1139/cjpp-2013-0445
4. Yang Q, Lei D, Huang S, et al. Effects of the different-sized external stents on vein graft intimal hyperplasia and inflammation. Ann Transl Med. 2020; 8(4): 102. https://doi.org/10.21037/atm.2020.01.16
5. Wan S, Arifi AA, Chan MCW, et al. Differential, time-dependent effects of perivenous application of fibrin glue on medial thickening in porcine saphenous vein grafts. Eur J Cardiothorac Surg. 2006; 29(5): 742-6; discussion 747. https://doi.org/10.1016/j.ejcts.2005.12.059
6. Kahraman N, Yumun G, Gücü A, et al. Administration of perivascular cyanoacrylate for the prevention of cellular damage in saphenous vein grafts: an experimental model. Cardiovasc J Afr. 2016; 27(3): 159-63. https://doi.org/10.5830/CVJA-2015-078
7. Dai L, Gao M, Gu C, Zhang F, Yu Y. Perivenous application of cyanoacrylate tissue sealants reduces intimal and medial thickening of the vein graft and inflammatory responses in a rabbit model of carotid artery bypass grafting. Eur J Cardiothorac Surg. 2016; 49(2): 675-81. https://doi.org/10.1093/ejcts/ezv111
8. Ip JH, Fuster V, Badimon L, Badimon J, Taubman MB, Chesebro JH. Syndromes of accelerated atherosclerosis: role of vascular injury and smooth muscle cell proliferation. J Am Coll Cardiol. 1990; 15(7): 1667-87. https://doi.org/10.1016/0735-1097(90)92845-s
9. Bhamidipati CM, Coselli JS, LeMaire SA. BioGlue in 2011: what is its role in cardiac surgery? J Extra Corpor Technol. 2012; 44(1): P6-12.
10. Azadani AN, Matthews PB, Ge L, et al. Mechanical properties of surgical glues used in aortic root replacement. Ann Thorac Surg. 2009; 87(4): 1154-60. https://doi.org/10.1016/j.athoracsur.2008.12.072
11. Stooker W, Niessen HWM, Wildevuur WR, et al. Perivenous application of fibrin glue reduces early injury to the human saphenous vein graft wall in an ex vivo model. Eur J Cardiothorac Surg. 2002; 21(2): 212-7. https://doi.org/10.1016/s1010-7940(01)01121-6
12. Khan H, Chaubey S, Desai J. Early failure of coronary artery bypass grafts: an albumin cross-linked glutaraldehyde (BioGlue) related complication. J Card Surg. 2011; 26(3): 264-6. https://doi.org/10.1111/j.1540-8191.2011.01208.x
13. Okazaki Y, Takarabe K, Murayama J, et al. Coronary endothelial damage during off-pump CABG related to coronary-clamping and gas insufflation. Eur J Cardiothorac Surg. 2001; 19(6): 834-9. https://doi.org/10.1016/s1010-7940(01)00708-4
14. Slezak P, Klang A, Ferguson J, et al. Tissue reactions to polyethylene glycol and glutaraldehyde-based surgical sealants in a rabbit aorta model. J Biomater Appl. 2020; 34(9): 1330-40. https://doi.org/10.1177/0885328219900078