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Evaluating the Outcome of Cardiovascular Surgery with Applying Tissue Patch; an Outstanding Alternative Novel Material in the Field of Cardiovascular Surgery

S Zeraatiannejaddavani, MD[1,2] , D Pazooki, MD, PhD[3,4*], N Kamalzadeh, MD[5], Mohammadali Yousefnia, MD, PhD[6], M Hosseini, MD[7], M Shams MD[7] and AJ Khamooshi, MD[6]

[1]Attending Professor of Cardiovascular Surgery and Dean of Faculty of Transplant and Organ Donation, Iran University of Medical Sciences, Tehran, Iran
[2]Northwestern University, Chicago Illinois, USA
[3]Professor(Guest) of Cardiovascular Surgery, Iran University of Medical Sciences, Tehran, Iran
[4]Department of Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden
[5]Cardiovascular Surgery and Transplant and Organ Donation, Iran University of Medical Sciences, Tehran, Iran
[6]Professor of Cardiac Surgery, Iran University of Medical Sciences (IUMS), Iran
[7]General Surgery, Iran University of Medical Sciences, Tehran, Iran

[*]**Corresponding author:** David Pazooki, MD, PhD, Department of Surgery and Cardiovascular & Thoracic Surgery, Hazrat Rasol Akrm Hospital, Iran University, Tehran Iran, Tel: +98-912-6773-808, E-mail: Pazooki.d@iums.ac.ir; Davood.Pazooki@vgregion.se

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1. Introduction

Definition: Intraoperative haemostasis is of paramount importance in the practice of cardiovascular surgery. Over the past 70 years, topical haemostatic methods have advanced significantly and today we deal with various haemostatic agents with different properties and different mechanisms of action. The particularity of coagulation mechanisms after extracorporeal circulation, has encouraged the introduction of new types of topic agents to achieve haemostasis, where conventional methods prove their limits [1]. Severe or massive bleeding in cardiac surgery is an uncommon but important clinical scenario. Its existing definitions are diverse. Its characteristics constantly change during an active hemorrhage and thus it is difficult to define appropriately. Cardiovascular surgery carries the highest risk of postoperative bleeding. Postoperative bleeding can lead to requiring more blood transfusion, reoperation, longer hospitalization, or higher mortality [2]. Intraoperative and postoperative hemorrhage is a relatively common event during and after open heart procedures, performed with extracorporeal circulation and various degrees of hypothermia. The average incidence is 5-9%, with limits between 0-16%, of all unselected cardiac surgical patients [3,4]. We performed a literature search to retrieve data that could contribute to answering clinical questions on the definition and grading of severe hemorrhage and massive transfusion, identifying factors that predict and affect bleeding and transfusion-related mortality and describing the risks of re-exploration and the economic impact of severe bleeding in cardiac surgery [5]. First preventive actions to control the bleeding during the operation include staples, sutures ligation, cauterization, and manual compression. However, some of these approaches are associated with creating needle holes and can cause further bleeding. In addition, manual compression may lead to injury and tissue trauma. The second line to control the bleeding involves utilizing hemostatic agents, tissue sealants, and adhesives. These methods may overlap with each other in terms of material, efficiency, or mechanism [4].

2. Hemostatic Agents

Hemostasis, the arrest of bleeding, requires a finely tuned balance between clot formation and clot degradation. Platelets provide the first line of defense when vascular integrity is compromised. They come home to the site of injury where they adhere to the damaged vessel wall, become activated and aggregate to form a platelet plug. The second line of defense involves the strengthening and stabilization of the platelet plug by fibrin strands, which tie the platelet aggregates together and render the hemostatic plug resistant to degradation. Fibrin strand formation is the culmination of the coagulation pathway, which is initiated by tissue factors exposed to the blood when the vessel is injured. Thus, the connective tissue surrounding blood vessels, the adventitia, is rich in tissue factors. Damage to the outside of the vessel disrupts this hemostatic envelope and triggers a series of connected reactions that culminate in a burst of thrombin generation. Through limited proteolysis, thrombin converts soluble fibrinogen into fibrin monomers, which then polymerize to form the fibrin protofibrils that give thrombi their 3-dimensional structure. Thrombin also serves as a potent platelet agonist that recruits additional platelets into the platelet-fibrin thrombus. Therefore, platelet responsiveness to external stimuli and rapid generation large amounts of thrombin are essential for effective hemostatic plug formation at sites of vascular injury.

The third and final line of defense at sites of vascular compromise involves the degradation of the hemostatic plug once it has served its barrier function. This pathway is initiated when the tissue-type plasminogen activator released from the damaged vessel wall converts plasminogen to plasmin. Plasmin degrades the fibrin strands into soluble fragments, thereby dissolving the hemostatic plug and restoring the vessel to its native state. Therefore, integration of this fibrinolytic pathway with the processes involved in clot formation is essential for maintenance of vascular integrity.

Thrombosis occurs when a clot forms inside a vessel instead of where the vessel wall has been breached by injury. Thrombosis can occur in arteries or in veins. Arterial thrombosis is the underlying cause of most heart attacks and strokes, whereas venous thrombi in deep veins, the so-called deep vein thrombosis, can break off and travel to the lungs to produce a pulmonary embolism. Therefore, it is not surprising that tremendous efforts have been made to better understand the pathophysiology of thrombosis and to develop antiplatelet drugs and anticoagulants to prevent and treat this common and potentially life-threatening condition. The mechanism of most hemostatic agents is facilitating tissue healing by creating mechanical bonds. These agents activate the extrinsic coagulation cascade and form a blood clot at the bleeding site to stop the bleeding.

There are 4 categories of hemostatic agents including:

1. **Mechanical agents**
2. **Flowable agents**
3. **Synthetic fibrin**
4. **Active sealants**

Mechanical agents: Such as gelatin-based, bovine collagen-based, cellulose-based, chitin and chitosan-based, and polysaccharide sphere agents act as a mechanical barrier by forming a platelet aggregation. Gelatin-based agents are Surgifoam, Gelfoam, and Gelfoam Plus. Examples of bovine collagen-based agents are Ultra foam Collagen Sponge and Avitene sheet. Surgicel and Surgicel Nu-Knit are used as cellulose-based agents. QuickClot, Celox, and HemCon are chitin and chitosan-based agents. Finally, Arista is an example of polysaccharide sphere agents [6,7].

Flowable agents: Including gelatin and gelatin matrix-thrombin-based agents such as Surgiflo and Floseal are microfibrillar collagen that convert fibrinogen to fibrin and clog the bleeding site [8].

Synthetic fibrin: Is made out of either fibrin-thrombin such as Evicel and Tissel or cyanoacrylate such as Glubran2 (GEM) [9].

Active sealants: Fibrin sealants are made of a combination of thrombin and fibrinogen. These sealants may be sprayed on the bleeding surface or applied using a patch. Surgical sealants might be made of glutaraldehyde and bovine serum albumin, polyethylene glycol polymers, and cyanoacrylates. Sealants are most often used to stop bleeding over a large area.

If the surgeon wishes to fasten down a flap without using sutures, or in addition to using sutures, then the product used is usually medical glue. The form a blood clot at the site of bleeding by breaking down the fibrinogen. This type of sealants is categorized into 3 groups including human pooled plasma-thrombin-based such as Evithrom, bovine-thrombin-based such as Thrombin-JMI, and recombinant-thrombin-based such as Recothrom.

2.1. Tissue sealants

Tissue sealants can control the bleeding without triggering the coagulation cascade. This type of sealants can be made out of fibrin such as Evicel and Tissel, albumin and glutaraldehyde such as Coseal and Duraseal, or polyethylene glycol polymer such as Omnex.

2.2. Tissue adhesives

Tissue adhesives end the bleeding through forming adhesive bonds at the site of bleeding. Fibrin-based tissue adhesives are such as Evicel and Tissel. However, they can be made out of albumin and glutaraldehyde such as Bioglu. Finally, their material can be cyanoacrylate such as Histoacryl and Glubran 2 (GEM).

Topical hemostatic agents are commonly used in a wide variety of surgical procedures to assist in hemostasis. However, the use of these agents is not without risk as many contain biologically active agents derived from human and animal products that have the potential to cause adverse reactions [10].

All above-mentioned products have several common advantages and disadvantages based on their material. Although fibrin-based products show good biocompatibility, biodegradability, elasticity, and low toxicity, they can cause disease transmission due to their animal sources.

Moreover, due to the thrombus formation, using these products poses high risk of acute thrombosis at the site of

surgery, embolization at distal sites and correlated complications.

PEG-based materials are degradable and bioabsorbable; however, they can cause swelling and damage to the surrounding organs. Products consisting of albumin and glutaraldehyde can also cause disease transmission due to their animal sources. Furthermore, due to high cytotoxicity of glutaraldehyde, tissue fibrosis at the application site leads to tissue hardening.

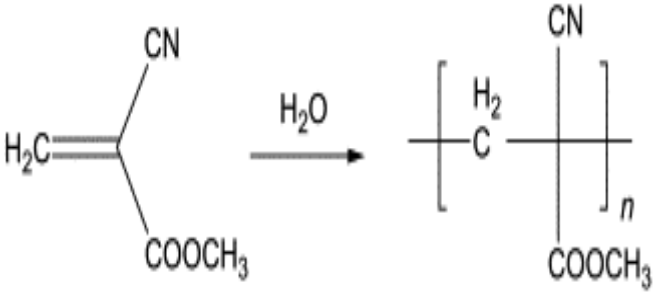
This event results in decreasing elasticity and vessel compliance, and subsequently vessel stiffness may happen. In addition, due to adhesion and fibrosis at the site of surgery caused by these products, redoing the operation becomes more challenging and laborious.

Cyanoacrylates are bacteriostatic and decrease the chance of site infection. Additionally, their waterproof properties serve as a barrier against blood and fluid. However, their high cytotoxicity causes more adhesion and fibrosis formation. Moreover, it increases the chance of inflammatory response, and, in dynamic tissues, it decreases the dynamic properties.

Thrombin-albumin products are associated with severe swelling at the site of application and subsequently higher chance of tissue damage. The α-cyanoacrylates polymerize by an anionic mechanism in the presence of water (Figure 1).

Higher alkyl derivatives polymerize more rapidly. The cyanoacrylates when exposed to normal level of humidity in the air cause polymerization rapidly. Because of this property, α-cyanoacrylate is applied thinly to ensure that reaction proceeds rapidly and forms a strong bond within a reasonable time [11].

Figure 1: Polymerization of α-cyanoacrylate.



To the best of our knowledge and due to the above-mentioned disadvantages, none of the discussed products has fully resolved the bleeding and associated complications during surgeries.

New products such as TissuePatch™ made from poly-lactic-co-glycolic acid have delivered outstanding results in controlling bleeding and decreasing the adhesion and air leakage during the thoracic and ear/head and neck surgeries.

Poly (lactic-co-glycolic acid) (PLGA) is a biodegradable functional polymer made from the polymerization of lactic acid (LA) and glycolic acid (GA) and is widely used in pharmaceuticals and medical engineering materials because of its biocompatibility, non-toxicity, and good plasticity [12].

Given the fact that there is no research focusing on the effect of application of TissuePatch™ on highly dynamic cardiovascular tissues, in this study, we investigate the results of using this product in various categories of cardiac surgeries [13].

3. Material and Methods

The present study is a randomized clinical trial on 694 open heart surgery cases between 2014 and 2021 at Rasool Akram Hospital affiliated to Iran University of Medical Sciences under supervision of OPOIUM. This study was designed to evaluate the result of cardiac surgery with application of TissuePatch™ and compare with the same cases without using TissuePatch™. The obtained data was compared with global cardiac surgery statistics in terms of postoperative bleeding (amount of drainage), the timing of drain removal, prevalence of pericardial effusion after drain removal, hospitalization duration, mortality rate, rate of rethoracotomy or redo operation for early bleeding.

This research was conducted under the approval of the Scientific and Ethics Committee of Iran University of Medical Sciences.

In this study, 694 patients who were candidates for open heart surgery including 360 cases of Coronary Artery Bypass Grafting (CABG), 60 Pediatric cases in which redoing the operation is inevitable, 40 Pediatric patients with single ventricle, 20 Patients with constrictive pericarditis, 20 Patient with malignant mesothelioma, 40 cases of penetrating heart trauma with simultaneous injury to lung and patients who have undergone heart and lung repair, 10 Bentall procedure, 100 valve surgeries (mitral valve replacement and AF ablation procedure), 20 cases of pulmonary valve and trunk reconstruction, 20 cases of tricuspid valve replacement, and 20 cases with cardiac transplantation with 'first LA to LA anastomosis technique'. The terms and goals of the study were explained to the patients and those who declined to participate were excluded. After obtaining informed written consent, the participants were randomly divided into two equal groups.

690 patients were candidates for open heart surgery. The follow-up echocardiography was conducted **immediately**, **3 months**, **6 months**, and **12 months** after the surgery.

Type of Cardiac Surgery	**Number**
CABG	360
Pediatric cases in which redoing	60
Pediatric patients with single ventricle	40
Constrictive pericarditis	20
Penetrating heart lung trauma	24
Bentall procedure	10
Valve surgeries (mitral valve replacement and AF ablation procedure)	100
Pulmonary valve and trunk reconstruction	20
Cases of pulmonary valve and trunk reconstruction Cardiac transplantation with 'first LA to LA anastomosis technique'	20 20
All participants in this study underwent an operation by one surgeon.	
Totalt	694

Cardiac MRI were utilized for assessment of 30 cases which result confirmed the transthoracic echocardiography, in other words no pericardial thickening,
Hematoma and other cardiac surgery complications were observed in cardiac MRI.

A questionnaire was completed for each participant regarding the demographic information (age and gender) and comorbidities, type of surgery, postoperative bleeding (amount of drainage), the timing of drain removal, amount of pericardial effusion after drain removal, the duration of hospitalization, mortality rate, rate of rethoracotomy, or redo operation for early bleeding. After collecting the data, the results of each surgery in the case group were compared with the same surgery in the control group.

All participants in this study underwent an operation by one surgeon. The follow-up echocardiography was conducted **immediately**, **3 months**, **6 months**, and **12 months** after the surgery. Additionally, cardiac MRI were utilized for assessment of 30 cases which resulted confirmed the transthoracic echocardiography, in other words no pericardial thickening, hematoma and other cardiac surgery complication were observed in cardiac MRI.

4. Results

The results were obtained from 694 cardiac surgery candidates who referred to Rasool Akram Hospital and were eligible for the study. In Coronary Artery Bypass Grafting (CABG) surgeries, pediatric surgeries, constrictive pericarditis surgeries, malignant mesothelioma surgeries, simultaneous heart and lung surgeries, Bentall procedure, Valve surgeries, and cardiac transplantation, postoperative bleeding (amount of drainage), the timing of drain removal, amount of pericardial effusion after drain removal, the duration of hospitalization, mortality rate, rate of rethoracotomy or the need to redo operation for early bleeding were significantly low incase group compared with control group. Moreover, in pediatrics surgeries, less adhesion was observed in case group than control group based on surgeon discretion during redo operations.

5. Discussion and Conclusions

In the introduction, bleeding control products along with their forms, materials, advantages, and disadvantages were discussed. In this section, the reported complications from clinical cases after using such products in cardiac surgeries are discussed.

Mohamed F. Ibrahim, et al. reported a 53-year-old woman with aortic valve regurgitation who underwent AVR surgery. After one year, she was diagnosed with dyspnea grade 4 again and underwent another operation for valve replacement.

Intraoperatively, the pus and apiece of non-absorbable Surgical were removed and sent to the microbiology and Gram stain. The results showed growth of microorganisms. In this case, foreign body reaction to the non-absorbable Surgical in AV site mimicked an abscess in the AV site and led to the patient underwent reoperation [13].

Daisuke Kaneyuki, et al. reported a 65-year-old woman who was presented with suspected mediastinitis following redoing the Benetall procedure. In this case, intraoperative investigations demonstrated that the remaining non-absorbable Surgicel misdiagnosed with mediastinitis and led the patient to under an unnecessary reoperation [14].

Shokoufeh Hajsadeghi, et al. reported a 55-year-old man with large local pericardial effusion with compression effect on right ventricle in echocardiography 4 days after modified Bentall operation. In computed tomography, no leakage from Benetall tube graft was observed. The patient underwent reoperation. Intraoperatively, 100cc fluid was drained, however, the suspected hematoma was accumulated Surgicel in the graft site and no leakage was observed [15].

The results were obtained from 694 cardiac surgery candidates who referred to Rasool Akram Hospital and were eligible for the study.

The following section shows the novel indications of Tissue Patch in various types of cardiovascular surgeries:

TissuePatch™
1. **Coronary Artery Bypass Grafting (CABG):** As a result of epicardial lacerations during looking for deeply seated epicardial vessels TissuePatch™ applied showed. Promising results regarding reducing postoperative bleeding and pericardial effusion.
2. **Patients with distal vessel targets such as Obtuse Marginal Artery (OMA) or Left Circumflex Branch (LCX):** Following the rotation of the heart and commencing cardiopulmonary bypass and administration of cardoplegia. Rotation of the heart in order to have the best access into the target vessels can. epicardium and TissuePatch™ decreased the postoperative bleeding from this injured epicardium and promote healing. 3. **Pediatric cases in which redo operation was inevitable:** Applying TissuePatch™ reduced further adhesion band and formation. 4. **Pediatric patients with single ventricle:** Applying TissuePatch™ decreased further adhesion band and formation. 5. **Patients with constrictive pericarditis:** After pericardiectomy or waffle operation TissuePatch™ reduced epicardial raw area bleeding and postoperative adhesions. 6. **Patient with malignant mesothelioma:** TissuePatch™ prevented further possible complications, such as, adhesions, severe pericardial effusion that could end up in tamponade effect. 7. **Penetrating heart trauma with simultaneous injury to lung:** Usage of TissuePatch™ prevented further air leak. 8. **Patients who have undergone heart and lung repair:** Usage of TissuePatch™ prevented further air leak. 9. **Bentall procedure:** Use of TissuePatch™ instead of heavy hemostats. TissuePatch™ can avoid compression effect on graft anastomosis as well as reducing compression effect on tubular graft on proximal and distal ends. 10. **LIMA to LAD anastomosis bleeding:** Heavily calcified CAD and fragile RV tissue because of ageing process of patient. Could not apply more controlling stitches so TissuePatch™ was used as supporting layer. 11. **Patients with chronic mitral valve stenosis and AF rhythm who was candidate for MVR and AF ablation procedure:** Closed the left atrial roof and

used TissuePatch™ as a supportive layer.

12. **Discrete subvalvular resection and pulmonary trunk reconstruction:** After ideal wedge resection in order to close pulmonary trunk, used native pericardium supported. by TissuePatch™ layer, reducing possibility of further aneurysmal formation.
13. **Armamentarium of CV surgery:** Utilizing TissuePatch™ apply was completely feasible in an experienced hand even in a beating heart. There is a need for training.
14. **Beating replacement of valve in tricuspid position for valve bacterial endocarditis:** Could not complete atrial closure due to atrial valve infection. TissuePatch™ was used as an overlaying supportive layer.
15. **3VD and recent myocardial infarction in the territory of OM who undergone CABG:** Cardiac stabilizer applied, bleeding territory repaired and in order to prevent further bleeding from the epicardial laceration, overlaying TissuePatch™ was applied and hemostasis performed.
16. **After cardiac transplantation with 'first LA to LA anastomosis technique:** In heart cases for the management of donor and recipient anastomosis bleeding which was not controllable. by further suturing the site simply sutured and TissuePatch™ was applied.
17. Bleeding from the epicardial laceration, overlaying TissuePatch™ was applied and hemostasis performed.

According to the results of this study, no complications correlating with usingTissuePatch™ were observed in the 345 studied patients.

Regarding the possibility for future complications such as empyema, pleural effusion and persistent air leak which necessitate long term follow ups, having a pulmonologist is highly recommended.

According to the results of this study, no complications correlating with using Tissue Patch™ were observed in the 345 studied patients. Moreover, a considerable reduction was observed in postoperative bleeding, the timing of drain removal, amount of pericardial effusion after drain removal, duration of hospitalization, mortality rate, rate of rethoracotomy or redo operations for early bleeding.

6. Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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8. Author Contribution

This study was conducted with the approval of the Scientific and Ethical Committee of Iran University of Medical Sciences.

S Zeraatiannejaddavani MD[1,3*] and D Pazooki MD PhD[3,4]

1. 1Attending Professor of Cardiovascular Surgery and Dean of Faculty of Transplant and Organ Donation, Iran University of Medical Sciences, Tehran, Iran .
2. 2Northwestern university, Chicago Illinois.
3. 3Professor of Cardiovascular Surgery Iran University of Medical Sciences, Tehran, Iran.
4. 4 Sahlgrenska University Hospital Department of Surgery, S-413 45 Gothenburg Sweden.

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