Could TachoSil application in cardiac surgery be potentially dangerous? A review of the literature

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Abstract

The application of TachoSil adhesive is becoming increasingly popular in surgical procedures. A special area of surgical medicine is cardiac surgery, where the adhesive makes it possible to provide hemostasis when classic anastomotic methods are insufficient. There are numerous studies available demonstrating the perioperative efficacy of TachoSil, and its ease of use in the human population. However, studies on the inflammation caused by TachoSil are widely limited to animal experiments. There is a lack of studies on human groups on TachoSil-induced inflammation in cardiac surgery. The purpose of our paper is to review the current knowledge on the use of TachoSil in animals and the incidence of inflammation, in order to determine whether there is a need for similar human studies in cardiac surgery. The paper discusses the details of this problem based on recent scientific reports.

Key words: TachoSil, cardiac surgery, adhesive sealants, hemostats in cardiac surgery.

Introduction

Cardiac surgery is particularly associated with the risk of patient blood loss. In order to reduce the need for blood transfusion or reoperation, and achieve hemostasis specifically in anatomical regions that are inaccessible to the operator (where standard surgical techniques are ineffective) or for additional wound sealing beyond surgical sutures, surgical adhesives are commonly used [1, 2]. Currently, there are three main groups of surgical adhesives: hemostats, adhesives and sealants. TachoSil, which has found application particularly in cardiac surgery, belongs to the group of adhesives [3]. TachoSil is a product developed by TachoComb (Nycomed Linz, Austria) and TachoComb H (Nycomed Linz, Austria). TachoComb consists of horse collagen, bovine thrombin and aprotinin, and human fibrinogen. However, TachoComb H contains human thrombin instead of bovine thrombin. The next improvement of this adhesive was the elimination of bovine proteins, so that TachoSil contains only human fibrinogen, with horse collagen acting as a carrier [4, 5]. TachoSil offers many advantages that favor its widespread use in cardiac surgery. One of the biggest advantages of TachoSil over other fibrin adhesives is the possibility to store it at room temperature. It does not need to be frozen or refrigerated, and it is ready for use once it is removed from the package, making it especially valuable in an emergency situation. In addition, it is relatively easy to apply compared to other surgical adhesives [4, 6]. TachoSil carries a lower risk of immune reactions compared to other hemostats such as Floseal or Gelofoam, due to the reduction of patient exposure to bovine genetic material [7]. In addition, TachoSil consists of biodegradable materials that minimize toxic effects on tissue, tissue injury and the risk of necrosis at the adhesive application site [8]. TachoSil is a surgical adhesive that has been approved for use by both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) [9]. TachoSil provides many advantages and is a very popular adhesive used in surgery in many different fields of medicine, so it is important to understand the potential dangers of its application. TachoSil is used in various surgical fields, such as liver surgery, cardiac surgery, and thoracic procedures [10]. The product promotes wound healing, improves bleeding control, and provides support during surgical suturing [11–15]. In cardiac surgery, TachoSil is used during: coronary artery bypass surgery, aortic aneurysm surgery, aortic bulb fixation in acute dissection, resection of heart tumors, surgical treatment of aortic valve stenosis, and ascending aortic dilatation [16–19].

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The purpose of this article is to present current reports on side effects resulting from the application of TachoSil in cardiac surgery. PubMed, PubMed Central and Google Scholar Web databases were searched using phrases related to: "TachoSil", "TachoSil-induced inflammation", "fibrin hemostats", "adhesive sealants in cardiac surgery" and "TachoSil cardiac surgery complications". After reviewing 50 abstracts, articles describing TachoSil research on appropriate experimental (mainly animal) groups were selected. The types of analyzed articles were original papers, meta-analyses, review papers, and case reports, and the language of the articles was English and Polish. Finally, the relevant paragraphs on TachoSil complications were created and comprehensively described.

TachoSil mechanism of action

TachoSil belongs to the group of adhesives, and its effects can be explained based on the literature describing the properties of fibrin sealants. Fibrin adhesives are hemostatic preparations that deliver fibrin and thrombin. Their mechanism of action is to convert fibrinogen into fibrin and form stable fibrin. They are widely used locally to control bleeding during endovascular and cardiac surgery, and to promote tissue bonding. Fibrin sealants include fibrinogen, fibronectin, factor XIII, thrombin, calcium and aprotinin. This combination allows simulation of the natural coagulation cascade. Thrombin and fibrinogen play a crucial role in clot formation. Thrombin converts fibrinogen to fibrin in the presence of calcium ions, and facilitates the fusion of calcium with factor XIII, leading to the formation of a fibrin reticulum. In addition, aprotinin helps to stabilize the clot [20, 21].

General complications of TachoSil use

There are research studies that describe side effects resulting from the use of surgical adhesives, which may potentially threaten patient health and life [22]. The main adverse effects of the adhesive may be related to immune reactions against TachoSil chemical compounds and to potential pathogen transmission [4]. As previously mentioned, the collagen used to make the glue can be derived from horse tendons, which can potentially trigger immune reactions [23, 24]. Additionally, it is possible to transmit parvovirus B19 from blood samples used in the production of the adhesive. Parvovirus B19 infection can result in the severe complication of aplastic crisis. Also, due to the possibility of parvovirus B19 transmission, the use of TachoSil during pregnancy is not recommended [25]. Studies demonstrating the effects of TachoSil use in cardiac surgery are largely limited to research performed on animal models. When considering the occurrence of inflammation, adhesions or fibrosis in the structures of the cardiovascular system, it is worth noting that the composition of TachoSil, as a thirdgeneration fibrin glue, has a minimal animal component (collagen extracted from horse tendons). The remaining components are fully of human origin. This significantly minimizes TachoSil contribution to the development of in-

54

flammation at application sites [26]. TachoSil also reduces the risk of possible difficulty in classical tissue anastomoses. In post-infarction cardiac wall rupture, due to the weakened myocardium and complicated conditions for the application of classical sutures, a sutureless procedure may be a better therapeutic option, as it eliminates the need for cardiopulmonary bypass and is more convenient for the surgeon. Various types of patches, such as autologous and xenologous pericardium, synthetic materials, extracellular matrix, or the described fibrin adhesives (TachoSil, Tacho-Comb), can be used as an alternative to classic sutures. Although tissue integrity is not disrupted with the use of TachoSil or TachoComb (as with conventional sutures or tissue patches), there is still a risk of re-rupture of the cardiac wall, formation of aneurysms and pseudoaneurysms. This risk is highlighted especially in "blow-out" ruptures of the left atrial free wall. At this time, there is a lack of longterm studies on the effectiveness of fibrin adhesives in ruptured cardiac wall repair surgery. Special vigilance and careful monitoring of patient postoperative condition are recommended when attempting to use this technique [27]. Yousef et al. concluded similarly, emphasizing the risk of re-rupture in "blow-out" mechanism and not recommending the use of TachoSil [28]. The literature also describes complications after TachoSil application in neurosurgery. In a study by Teixidor-Rodríguez et al., possible adverse effects were described as hydrodynamic disturbances of the cerebrospinal fluid in 5% of patients undergoing the study [29]. Complications of surgery and the primary disease themselves may also be misdiagnosed as side effects after TachoSil application: supraventricular arrhythmias, nausea, pleural effusion, hyperglycemia, anemia or fever [30].

TachoSil may cause tissue inflammation

In a study conducted by Okata et al. in August 2022, three products were compared: oxidized regenerated cellulose (SURGICEL), TetraStat and TachoSil, both in vitro and in vivo. In the in vivo experiment, rats' inferior venae cavae were pricked with 18- and 20-gauge needles and allowed to bleed. Although inflammatory reactions such as infiltration of inflammatory cells, granulation formation and fibrosis were noted after the application of each sealant, the TachoSil treatment group additionally showed the presence of a thrombus in the vena cava [31]. Recently, Tacho-Sil has become a popular solution in penile surgery, where it is used to cover defects in the tunica albuginea of the penis, which is associated with reported clinical success. In a study conducted by Seyam *et al.*, the histopathological effects of using TachoSil in surgery of the tunica albuginea in the rat penis were studied. Six adult male Sprague Dawley rats were involved in this experiment. Longitudinal cavities of the penis were made, and TachoSil was applied to them. After 2 months, the penises were removed, and specimens were obtained and analyzed under a microscope after appropriate preparation. Fibrosis, chronic inflammation, and foreign body giant cell reaction were observed. One of the examined rats died 6 days after surgery. Postmortem examination revealed massive multiorgan hemorrhage consistent with disseminated intravascular coagulopathy (DIC) [32]. Another study on the cellular effects of using TachoSil is the experiment by Hadavi et al. Thirty-six adult male rats were randomly separated into two groups: Group C (control group), in which a standard anastomosis was performed in the ileum 10 cm from the ileocecal valve, using an intermittent Vicryl 5-0 suture, and Group S (study group), in which an anastomosis was performed in the same area but with TachoSil using three sutures (mesenteric, anti-mesenteric, and anterior wall as a suture-less method). Their findings revealed that histopathologically, group C exhibited more cells associated with chronic inflammation, while group S exhibited more cells associated with acute inflammation. All the results suggest that more cases in group C progressed to the final stages of healing, while those in group S stopped at the initial stages. Based on microscopic examination of cadaveric sections of rats in group S that died before the set time of the experiment, the causes of death were determined to include: intravascular thrombosis, acute ileitis, ileal gangrene, microscopic peritonitis, vasculitis (with fibrin deposition in the vessel wall), and hypersensitivity reaction (eosinophilia). Macroscopic observation of the specimens showed that TachoSil separated from the anastomotic area and induced a strong inflammatory reaction and adhesions in all cases in group S [33].

TachoSil versus atherosclerosis

A study by Jaberi et al. discovered that thrombin has a multifunctional role as a proinflammatory, procoagulant and anticoagulant factor. It affects platelet activation and initiates clot formation by converting fibrinogen into fibrin. Its anticoagulant effect is revealed when it combines with thrombomodulin, leading to activation of protein C. Activated protein C inactivates factors Va and VIIIa, inhibiting blood coagulation. Thrombin is also an important regulator of various cell types, such as multinucleated leukocytes, monocytes, endothelial and smooth muscle cells. Its proinflammatory effects are further enhanced by increasing the expression of cell adhesion molecules such as ICAM-1 [34]. It should be noted that thrombin can also induce atherosclerotic processes through increased release of inflammatory mediators from activated cells in areas of inflamed vessels. In the context of using TachoSil, which is a sponge coated on one side with fibrinogen and thrombin, there is a risk of local inflammatory reactions and promoting atherosclerotic plaque formation at the site of adhesive application [4].

TachoSil vs aortitis and carditis

A study by Kuschel *et al.* performed on an animal model using rabbits reported a beneficial effect of TachoSil against the formation of postoperative pericardial adhesions. The results indicated reduced postoperative adhesion formation, as well as a reduced inflammatory response compared to a surgical membrane made of Gore-Tex [26]. Other animal studies have also shown a reduction in the incidence of postoperative scarring as a result of TachoSil application [5]. However, these conclusions are contradicted by a study by Erb et al. in which such a trend was not observed. A study based on analyzing the effects of TachoSil application in coronary artery bypass grafting (CABG) surgery showed that the adhesive induced a significant immune response in myocardial structures [35]. In this research, the authors divided 15 operated pigs into three experimental groups: A – control group, B – group with anastomosis covered with 1 ml of Beriplast fibrin glue (ZLB Behring, Bern, Switzerland), and C - group with anastomosis covered with TachoSil. Thirteen animals survived both the operation and the 3-month postoperative period without complications. Two intraoperative deaths were due to ventricular fibrillation prior to fibrin glue application, which was confirmed by observation of ST-segment elevation on the ECG, suggesting ischemia. No significant differences were observed in growth and weight gain in pigs from different groups. Analysis of operation time and blood loss showed no significant differences between groups. In all animals, sufficient blood flow was observed in the thoracic artery after anastomosis to the left anterior descending artery (LAD). Autopsy confirmed a perfectly healed sternotomy and the presence of pericardial adhesions. Histological examinations in most cases confirmed the patency of the left internal mammary artery grafts to the LAD. There was no histological evidence of morphological disruption of the intima due to the sealants used (TachoSil in group C or fibrin glue in group B), but fibroblast growth and the presence of scar tissue around the anastomosis were observed. The authors also point out that this relationship may be due to humanderived components, making it difficult to translate these results to a human model. However, the authors also add that due to this fact and the relatively short observation period, it can be assumed that the occurrence of a similar reaction in humans is rather unlikely [35].

Future directions

Inflammation in the affected tissue can manifest through vasodilation, increased capillary permeability, chemotaxis, diapedesis, leukocytosis, increased metabolic activity, edema, redness (rubor), heat (calor), pain, or fever [22]. Under regular conditions, these mechanisms should lead to regeneration of the affected area, while if the process is prolonged, it can lead to the development of chronic inflammation. A tissue sample can be obtained from the pathologically transformed region for histopathological examination to confirm the inflammation [36]. In addition, it is worth submitting the material to microbiological tests to detect the pathogen responsible for the infection [37]. The symptoms of inflammation can manifest in various forms, including the formation of pathological masses that cause pericardial tamponade, the formation of pseudoaneurysms, or the development of mediastinitis and vasculitis [22]. Therefore, we suggest collecting material for histopathological and microbiological examination from suspected inflamed cardiac tissues, mediastinum or pericardial vessels where TachoSil has been previously applied. The results of future prospective studies would provide valuable conclusions about TachoSil-induced inflammation in the human population.

Conclusions

TachoSil is a product that significantly facilitates surgical procedures. Its biodegradable formulation, as well as its mechanism of action involving the clotting cascade naturally occurring in the human organism, considerably determines its safety. However, based on the reviewed studies, it can be concluded that there is a correlation between the occurrence of inflammatory (inflammatory cell infiltration, granulation, acute inflammation at the application site) and thrombotic (DIC, thrombosis) complications with the application of TachoSil on animal groups. Because of the growing popularity of fibrin adhesives in practice and the insufficient number of studies confirming or excluding the existence of these correlations in humans, performing such studies in the human population seems a necessary next step to ensure the safety of TachoSil tissue adhesive in future.

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Ethical approval

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Disclosure

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