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REVIEW ARTICLE

The use of state-of-the-art haemostatic materials in gastrointestinal surgery

Wykorzystanie nowoczesnych materiałów hemostatycznych w chirurgii układu pokarmowego

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Manuscript Preparation
E – Literature Search
F – Funds Collection

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ABSTRACT: Haemostatic materials such as: gelatine sponges, oxygenated cellulose meshes, tissue sealants, collagen matrices with human thrombin and fibrinogen are gaining on popularity in gastrointestinal surgery, especially in colorectal surgery. We searched for available scientific publications in the Pubmed and Cochrane database on the use of individual hemostatic materials in the field of gastrointestinal surgery. The analysis focused on the assessment of the safety of the use of individual materials in terms of the rate of bleeding complications and the rate of anastomotic leakage cases. The use of haemostatic materials has for years been a recognized method of reducing the rate of intra- and postoperative complications, both in gastrointestinal surgery and in other surgical specialties. Based on the available studies, it can be concluded that the use of hemostatic materials such as matrices, sponges and adhesives in gastrointestinal surgery, even in patients at high risk of anastomotic leakage and bleeding complications, reduces the incidence of complications. The growing popularity of haemostatics and sealants in surgery means that they are currently used in a wide range of indications, and surgeons are more and more willing to use them even in case of standard surgical procedures, which is reflected in the available studies. Choosing a haemostat should be a conscious decision, taking into account the site and type of bleeding, mechanism of action, ease of use, efficacy, safety, and price, among others.

KEYWORDS: anastomotic leak, haemostatic agents, hemostasis

STRESZCZENIE: Materiały hemostatyczne, takie jak: gąbki żelatynowe, siatki z utlenowanej celulozy, kleje tkankowe, matryce kolagenowe z ludzką trombiną i fibrynogenem, zyskują coraz większą popularność w chirurgii układu pokarmowego, zwłaszcza w chirurgii kolorektalnej. Wykonano kwerendę dostępnych publikacji naukowych w bazach Pubmed i Cochrane dotyczących wykorzystania poszczególnych materiałów hemostatycznych w zakresie chirurgii przewodu pokarmowego. W analizie skupiono się na ocenie bezpieczeństwa użycia poszczególnych materiałów w kontekście odsetka powikłań krwotocznych i odsetka nieszczelności zespolenia jelitowego. Wykorzystanie materiałów hemostatycznych od lat jest uznaną metodą zmniejszenia odsetka środ- i pooperacyjnych powikłań zarówno w chirurgii przewodu pokarmowego, jak i w innych specjalnościach zabiegowych. Na podstawie dostępnych badań, można stwierdzić, że zastosowanie w chirurgii układu pokarmowego materiałów hemostatycznych, takich jak: matryce, gąbki i kleje, nawet u pacjentów w grupie wysokiego ryzyka nieszczelności zespolenia i powikłań krwotocznych pozwala na redukcję częstości występowania powikłań. Rosnąca popularność hemostatyków i uszczelniaczy w chirurgii sprawia, że obecnie wykorzystuje się je w szerokim wachlarzu wskazań, a chirurdzy coraz chętniej sięgają po nie nawet w przypadku standardowych procedur zabiegowych, co znajduje odzwierciadlenie w dostępnych badaniach. Wybór hemostatyku powinien być świadomą decyzją uwzględniającą m.in.: miejsce i rodzaj krwawienia, mechanizm działania, łatwość użycia, skuteczność, bezpieczeństwo i cenę.

SŁOWA KLUCZOWE: hemostaza, materiały hemostatyczne, nieszczelność zespolenia

ABBREVIATIONS

BMI – body mass index
EBM – evidence-based medicine
HIPEC – hyperthermic intraoperative intraperitoneal chemotherapy
NHS-PEG – pentaerythritol poly(ethylene glycol) ether tetrasuccinimidyl glutarate
PEG – poly(ethylene glycol)
TME – total mesorectal excision

INTRODUCTION

Intraoperative bleeding is an important factor affecting the risk of complications such as surgical wound infection (secondary to hematoma or seroma formation within the wound), hypovolemia, or anemia. In addition, proper hemostasis reduces the duration of drain placement, reduces the risk of respiratory disturbances, and shortens hospitalization time while reducing hospitalization costs [1, 2]. Obtaining proper hemostasis is a prerequisite for success of all surgical procedures while allowing to avoid a number of intra- and post-operative complications.

Factors with negative impact on hemostasis may be patient-dependent. These include e.g. the intake of oral anticoagulants, other coagulation disorders or metabolic diseases, stage and grade of the disease, surgical site location, and presence of adhesions extending the duration of surgery and increasing the risk of bleeding. On the other hand, patient-independent unfavorable prognostic factors include the mode of surgery (i.e. as performed in emergency

setting), inappropriate experience of the surgical team regarding the application and monitoring of hemostasis, lack of access to state-of-the-art equipment such as argon coagulation, harmonic knives, hemostatic materials such as sealants or fibrinogen and thrombin matrices. Wherever possible, the surgeon should have a number of hemostatic tools available in their armamentarium since various intraoperative settings and complications may require different, frequently sophisticated solutions to achieve optimum hemostasis. Quite commonly, standard methods used to stop bleeding such as vessel pinning and ligation, electrocautery, argon coagulation, or clipping, are insufficient or ineffective.

To address the needs of intraoperative hemostasis, a number of local hemostatic agents were developed. These are classified into: (1) mechanical (passive) hemostatics – gelatin sponges, collagen sponges, oxygenated cellulose-based products and (2) active hemostatics which support physiological hemostasis and contain tissue-derived components such as albumin, fibrinogen, and thrombin. A separate group consists of synthetic agents used for sealing and hemostasis such as Poly(ethylene glycol) (PEG), cyanoacrylates, or glutaraldehyde. Combined products derived from synthetic and organic agents, such as albumin and glutaraldehyde, are also available. Numerous other classifications can be found in the monographs on hemostatic agents to reflect their different compositions (organic, synthetic), forms (liquid, solid), mechanisms of action (passive/mechanical, and active), or registration status (medical devices, medicinal products). This study focuses on the analysis of the safety and efficacy of selected local hemostatics as used in the surgery of the digestive system including liver surgery, pancreatic surgery, and gastrointestinal tract surgery. The efficacy of the currently available hemostatic agents regarding the control of bleeding is comparable to that of e.g. surgical diathermy [3]. Furthermore, reports are available showing that some hemostatic materials, such as TachoSil® (Takeda), are superior to argon coagulation when providing hemostasis in liver surgery [4].

The authors of this study reviewed the available literature published prior to 2021. Included in the analysis were the results of studies listed within the PubMed, Cochrane, and Embase databases. The following keywords were used to query the databases: hemostatics, hemostatic materials, hemostasis, fibrin sponge, anastomotic leak. The analysis included high evidence-level studies published in Polish and English, with particular focus on studies comparing individual groups of hemostatic materials. In addition to studies aimed at demonstrating the safety of particular hemostatic materials in the context of their clinical use, studies focusing on the use of these hemostatic materials to prevent bleeding or anastomotic leaks were also included. Overall, a total of 49 studies were included in this literature review.

MECHANISM OF ACTION

Besides its ability to stop bleeding which as a result of mechanical sealing of tissues or by activation of specific agents within the coagulation cascade depending on the material used, an ideal hemostatic agent should be biocompatible and biodegradable, present with adhesion capability in a humid environment, be non-toxic, and present with appropriate mechanical properties facilitating shape remodeling and tissue mobility following application. The cost and the ease of use of the material are also important. To date, hemostatic materials found their practical use in numerous areas of surgery such as general surgery, liver surgery, GI surgery (particularly colorectal surgery), neurosurgery, cardiac surgery, thoracic surgery, pediatric surgery, ophthalmology, urology, dentistry, vascular surgery, gynecology and obstetrics, as well as plastic and reconstructive surgery. Selected hemostatic materials are also increasingly used for tissue and organ sealing [4–6].

Mechanical hemostatic materials of organic origin such as collagen and gelatin sponges or cellulose grids are composed of proteins or polysaccharides. Their properties facilitate passive hemostasis and promote the healing process. The mechanism of action of these materials consists in providing a mechanical support for clot formation. On the other hand, the mechanism of cation of tissue-derived active materials such as collagen matrices with fibrinogen and thrombin, or tissue sealants, consists in the triggering of natural coagulation cascades, particularly its last stages involving thrombin being used to transform fibrinogen into an established clot [5, 6].

The first hemostatic materials consisted of cellulose and gelatin sponges. The first gelatin foam available in the market was GELFOAM® (Pfizer). Its task consisted in binding fibronectin for the adhesion of platelets prior to their subsequent activation. The second material to be introduced, and continuing to be widely used in surgery, was oxidized cellulose SURGICEL® (Ethicon). Both types of materials are inexpensive and easy to use.

Other, more sophisticated materials include synthetic hemostatic agents or combined organic and synthetic agents. Their mechanism of action consists in creating a mechanical barrier owing to their structure and composition. Examples of such materials include the pegylated collagen sponge HEMOPATCH® (Baxter Healthcare), or oxidized cellulose coated with pentaerythritol poly(ethylene glycol) ether tetrasuccinimidyl glutarate (NHS-PEG) VERISET®(Medtronic). According to many authors, these agents ensure efficient mechanical sealing of anastomoses or effective stopping of bleeding. In addition, the materials are resilient and present with strong adhesive properties. Their use is effective in the particular settings [7–9].

THE USE OF HEMOSTATIC MATERIALS

Currently, one of the most popular hemostatic materials is TachoSil®, consisting of a collagen matrix coated with human fibrinogen and thrombin. Its mechanism of action is exerted by the combination of mechanical properties responsible for creating a barrier preventing gases and liquids from passing through, and the effect of the active agents fibrinogen and thrombin triggering the last stages of the physiological coagulation cascade. As the result of this action, thrombin converts the fibrinogen into fibrin monomers which then polymerize spontaneously to form a fibrin clot. As the result, the collagen matrix tightly adheres to the wound surface. When the matrix is placed at the destination site, fibrin is cross-linked by endogenous factor XIII to form a strong, mechanically stable reticulum with good adhesive properties additionally contributing to the final closure tightness. The matrix is subject to enzymatic degradation and phagocytosis within 12 weeks from being applied. TachoSil® is used both for bleeding stoppage as is a common practice in liver surgery, as well as for ensuring that anastomosis is sealed and tissues are protected from damaging external factors. The literature contains the reports on the use of TachoSil® within the gastrointestinal

tract, blood vessels, lymphatic vessels, dura mater, pancreas, lung tissue, or the bile ducts. It provides optimal healing conditions and strengthening of sutures in vascular surgery. Contraindications for use include hypersensitivity to human blood products and equine proteins. The product has a favorable safety profile as no immune reactions were reported to date in association with its use [4, 10, 11].

Besides the aforementioned standard uses, the search for new applications of TachoSil® is still on. An animal model was used to demonstrate the superiority of TachoSil® compared to synthetic mesh in inguinal hernia repairs in terms of reducing post-operative pain, the use of analgesics, and the rate of post-operative complications. In addition, studies on the efficacy of TachoSil® in intestinal anastomoses have been carried out in recent years [12–17]. Studies show that TachoSil® sponges reduce the demand for blood and blood product transfers thus reducing the rates of remaining post-operative complications [18].

Many studies demonstrated that the use of hemostatic materials is an important factor responsible for the reduction in the incidence of bleeding complications, particularly in patients at risk of increased intra- and post-operative bleeding. The results of available studies warrant the conclusion that TachoSil® sponges are safe and efficient in preventing anastomotic leaks in experimental animal models as well as in clinical practice. Observations regarding the safety of the product, its hemostatic efficacy as well as its beneficial effect on the healing of intestinal anastomoses were also confirmed in the studies conducted by the authors of this review [14–19].

LIVER SURGERY

Intra- and post-operative bleeding are one of the most important factors affecting the complication and mortality rates in liver surgery. Hemostatic agents finding their use in liver surgery include e.g. fibrin sealants (Tisseel™, Evicel™), human thrombin and fibrinogen sponges (TachoSil®, Tissucol™), gelatin sponges (Gelfoam™, Surgifoam™), collagen sponges (Helistat™, Hemopad Novacol™), cellulose sponges (Veriset™), and hemostatic powder sprays (Hemostase MPH, Duraseal™). They are used in laparoscopic as well as open surgeries. Numerous studies were published in the literature confirming the effectiveness of hemostatic materials and their impact on the reduction of complication rates [20].

The efficacy of TachoSil® sponges was first demonstrated in a study published in 2005. At that time, fibrinogen and thrombin-filled matrix was shown to be superior to argon coagulation in elective liver resections [21].

Another significant experience came from the study carried out in 115 patients to undergo partial liver resection who were divided into 2 groups: (1) the study group where TachoSil® matrix was used; and (2) the control group where no local hemostatic agent was used during the surgery. Findings in the study group included reduction in drainage volumes, reduced rates of blood and blood product transfers, lower rate of post-operative complications, and shorter hospitalization times [22].

In 2011, a multi-center prospective randomized study was published which ultimately confirmed the advantage of TachoSil® over argon coagulation. The time needed to achieve hemostasis using the TachoSil® matrix was shorter than in the case of argon coagulation [23]. The efficacy of this agent regarding the stoppage of biliary contents and blood leaks was also demonstrated for liver transplant surgeries [24]. In one study, it was even referred to as "a new Glisson surface". Recommendations include applying the hemostatic material with a 1- to 2-cm margin around the bleeding surface [25].

PANCREATIC SURGERY

Pancreatic resection surgeries are usually associated with a high risk of perioperative complications, even at reference centers. Postoperative pancreatic fistula is one of the most common and the most serious complications following partial pancreatic resections. However, the use of hemostatic materials in pancreatic surgery remains controversial. Orci et al. examined a group of 897 patients subjected to partial pancreatic resections in 7 studies. A statistically significant reduction in the percentage of postoperative bleeding as well as a reduction in the percentage of peritoneal fluid collections were observed following the use of the fibrin sealant. No differences in the mortality rates, surgical site infections, and duration of hospital stays were observed in another study. Fibrin sealant (Tisseel®) was not shown to reduce the incidence of pancreatic fistulas [26]. Also examined was the use of fibrin sealants for closing the pancreatic stump in order to prevent the formation of pancreatic fistula. An analysis of 11 studies carried out in a total of 1462 patients in whom fibrin sealants had been used showed no reduction in the pancreatic fistula incidence rates. In view of the studies carried out so far, fibrin sealants cannot be routinely recommended for pancreatic surgery [27, 28].

GASTROINTESTINAL SURGERY

Intestinal anastomotic leaks are one of the most important problems in colorectal surgery. Depending on the site and the study, the incidence of this complication ranges from 0.5% to 30%, with values in the range of 3% to 10% being reported in most cases. Very often, note was taken of the leaks occurring in low and ultra-low anastomoses following anterior rectal resection. In line with the Polish consensus on protective stomy, the most important risk factors for anastomotic risk following low anterior rectal resection included male sex, obesity, age of >57 years, smoking, alcohol abuse, European origin, vascular comorbidities, steroid therapy, anemia of <8 g/dL, intraoperative demand for blood transfer, hypoalbuminemia of <3.5 g/L, neoadjuvant therapy, low anastomosis located less than 3 cm from the pectinate line, and the use of immunosuppressants. Other factors associated with increased risk included the total mesorectal excision, positive anastomotic leak test and/or incomplete stapler tissue disks, surgery duration of >4 hours, significant intraoperative difficulties (e.g. very narrow pelvis, technical difficulties), cachexia – BMI (body mass index) of <19, ASA III or ASA IV burden and site performing less than 20 anterior rectal resections/surgeon performing less than 20 anterior rectal resections per year [29–31].

Individual pre- and intraoperative evaluation is extremely important for identification of patients in whom the risk of intestinal anastomotic leak is particularly high. These patients require special attention and care in terms of the surgical technique and the use of materials so as to ensure adequate tissue integrity. In recent years, TachoSil® has been increasingly used to secure intestinal anastomoses.

Parker et al. evaluated a group of 25 patients subjected to anterior rectal resection by means of open or laparoscopic surgery. In all cases, TachoSil® was found to be safe, with no post-operative complications being observed in direct relation to the use of the material, and no anastomotic leaks being detected [32].

Other authors argue that also aprotinin, fibrinogen, and thrombin--containing tissue sealants are effective in reducing the rates of anastomotic leaks, the costs associated with shorter hospital stays, and the rates of revision surgeries and blood or blood product transfers. In their opinion, this is due to the lower rates of anastomotic leaks. According to the cost analysis provided by Panda et al., the use of a fibrin sponge contributes to an average of EUR 897 being saved by reducing the anastomotic leak rates [33].

Tissue sealants appear to be a very practical solution for leak prevention, particularly in difficult anastomoses. In one prospective study in 70 patients undergoing resection involving a high risk anastomosis being formed in the colon, the study population was divided into two groups of 35 patients: (1) in the first group, anastomosis was formed using a single layer of extramucosal suture, whereas (2) in the second group, the same suture was used with the addition of fibrin sealant. In the fibrin group, leaks were observed in 8% (n = 3) of cases as compared to 20% (n = 7) in the non-fibrin group. Although the difference was statistically significant only at P = 0.3, a certain trend was demonstrated suggesting the need for further comparative studies on this subject. Ongoing discussions among the experts suggest that relevant studies are already being taken up in an increasing number of research sites, both in Poland and abroad. The authors of the above mentioned study stressed that the addition of fibrin mimics the final stages of the coagulation cascade. In addition, it provides mechanical reinforcement for the anastomosis [34].

Research publications demonstrate the usefulness of hemostatics in both animal studies where high-risk anastomoses were generated experimentally, and in everyday clinical practice in patients presenting with risk factors for anastomotic leaks.

The use of additional hemostatic materials is particularly important when anastomoses are associated with a high risk of leaks due to the primary disease or comorbidities. HEMOPATCH® was demonstrated to be effective in patients with peritoneal spread of cancer undergoing HIPEC with simultaneous cytoreductive surgery — no anastomotic leaks were observed in the study group [35].

Hemostatic materials are particularly useful in patients at high risk of post-operative complications [36]. In mice with bacterial peritonitis and/or leaking anastomoses being generated experimentally, anastomotic sealing and healing was observed after collagen matrix with thrombin and fibrinogen was used [37].

In addition to preventive use, it is also appropriate to use hemostatic matrices in the treatment of a confirmed anastomosis leak, e.g. following low anterior rectal resection. In a specific group of patients in whom surgical treatment is not absolutely necessary (patients without fluid collections within the peritoneum, patients without septic markers, patients with protective stomy), fibrin can be introduced to the site where the anastomotic leak occurred by means of endoscopic techniques. The safety of this type of leak management was confirmed in research studies [38].

Also interesting is an experimental model including 40 malnourished rats in whom colon ischemia had been induced by partial vasculature ligation and the colon was perforated for subsequent application of TachoSil®. As the result of this experimental, animal model of colon perforation, the usefulness and efficacy of hemostatic matrices was demonstrated [39]. Other animal models demonstrated the usefulness and efficacy of a tissue sealant (TISSEEL®, Baxter Healthcare) as used for surgical anastomoses even in uncontrolled diabetes [40].

In recent years, the use of hemostatic materials in everyday surgical practice and in other procedural specialties has become increasingly common as confirmed by the increasing number of scientific studies published on this subject. In addition, a growing number of publications compare the efficacy of different materials. Albeit high-evidence level studies remain scarce, many researchers believe that TachoSil® is one of the best studied and most effective hemostiatics and sealants as used in various procedural specialties [41–44].

TachoSil® was also used in upper gastrointestinal tract surgeries, such as in total gastrectomy, esophagectomy, or esophagojejunostomy [45].

In colorectal surgery, numerous uses other than those listed above were also found for topical hemostatic agents, including in the treatment of intestinal, anal, gastrocutaneous, esophagogastric, gastrointestinal, peritoneal, and inguinal fistulas. The efficacy of the treatment for individual types of fistulas ranges from 0% to 100% [30, 46]. With no doubt, the problem requires further intensive research.

It is suggested that fibrin sealants might be useful for the closures of large anal fistulas (longer than 3.5 cm) due to the difficult surgical access promoting the use of less invasive therapeutic methods [47].

In endoscopic procedures, "hemostatic powders" can be used to control bleeding from the upper gastrointestinal tract. An example is provided by the HemoSpray® powder (CookMedical, Bloomington, USA) which absorbs water from blood while turning into a gel providing a mechanical barrier to the bleeding [48].

However, limitations due to the scarcity of high-evidence level studies should be borne in mind. In some analyses no benefits of hemostatic agents could be demonstrated for intestinal anastomoses (a rat study involving the use of a fibrin sealant) [49]. Numerous studies are still in progress. It is to be hoped that new evidence-based solutions emerge within about 2 to 3 years.

SUMMARY

Correct surgical technique is one of the most important factors which determine the success of the surgery. It contributes to reducing the risk of intra- and post-operative complications. In special cases where adverse patient-dependent or patient-independent factors are at play, local hemostatic and sealing agents may be required. The choice of a hemostatic agent should be made by the surgeon in an informed manner by taking into account the location and type of bleeding, the mechanism of action of the hemostatic agent, the ease of its use, its effectiveness, safety, and price. The availability of new hemostatic and sealing agents for the digestive system surgery contributes to the improvement in the surgical technique. Hemostatic materials have been applied in virtually all procedural specialties. Studies to date have confirmed they are safe while facilitating

avoidance of potential hemorrhagic complications and anastomotic leaks in gastrointestinal surgery. The authors hope that further reports will confirm the usefulness of hemostatics, particularly in colorectal surgery, and will contribute to the improvement in treatment results with regard to the rate of intestinal anastomotic leaks. Collagen matrix coated with fibrinogen and thrombin is one of the best examined and most effective local hemostatic and sealing products as used in various procedural specialties.

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