Chapter

The Use of Biomaterials in Gastrointestinal Endoscopy

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Abstract

Gastrointestinal endoscopy has evolved to become a therapeutic resource for multiple pathologic conditions, utilizing many techniques, tools and materials from the field of conventional surgery. Thermal, mechanical or chemical modalities are often employed to expedite the process of hemostasis and achieve a stable coagulum. Thermocoagulation coupled with devices for mechanical hemostasis have been adapted successfully to endoscopy. Chemical hemostasis from biomaterials can be obtained from biologically active materials such as thrombin and fibrin, absorbable products such as gelatins, collagen and oxidized cellulose or synthetic products and inorganic powders. Aside from hemostatic properties, biomaterials are also appealing due to its ability to promote wound healing. However, the use of biomaterials has not been as widespread in endoscopy as in conventional surgery, mainly because of the constraint of delivering these materials through an endoscope. Over the last decade, the options for biomaterials have expanded and its incorporation in endoscopy has slowly increased. Although the cost of biomaterials is higher compared to traditional hemostatics, this may be offset by the potential benefits of decreased bleeding related complications, procedure time, hospital stay and blood transfusions. Biomaterials have demonstrated an improvement in clinical outcomes during conventional surgery. Nevertheless, more studies are required to extrapolate these benefits to endoscopy.

Keywords: biomaterials, endoscopy, hemostasis, thrombin, fibrin sealant, gelatin, oxidized cellulose, collagen, acrylate polymers, hemostatic powders

1. Introduction

Although endoscopy can be traced back to ancient Greece, the Lichtleiter invented by Bozzini in 1805, is one of the earliest descriptions of endoscopy and established the basis of current endoscopy [1]. Further developments include the development of flexible endoscopes. However, endoscopy did not become widespread until the invention of the fiber optic endoscope in the 1960s [2]. Endoscopic ultrasound (EUS) was developed in 1980 and constituted another innovatory development of endoscopy [3].

Initially a purely diagnostic procedure, gastrointestinal (GI) endoscopy has evolved to become a therapeutic resource for multiple pathologic conditions, utilizing many of the techniques, tools and materials successfully employed in

conventional surgery. A current advancement is natural orifice transluminal endoscopic surgery (NOTES) or incisionless surgery. First described in 2004, it uses endoscopic equipment to perform surgical procedures using natural orifices to access the peritoneal cavity, also known as "second space". However, safe closure of the point of entry has been a concern. More recently, another concept developed in 2007 and known as "third space" or submucosal endoscopy, has allowed access to the submucosal or intramural space, creating a mucosal safety valve, addressing one of the concerns of NOTES [2, 4].

Endoscopic surgery demands knowledge, skills and judgment that spans both surgery and gastroenterology training. It requires good knowledge of the pathophysiology of the diseases, exceptional endoscopic skills, an in-depth understanding of the anatomy, as well as the ability to manage the potential adverse events associated with the procedure. The standardization of technique has allowed to reduce the complexity associated with these procedures, currently being performed mostly in endoscopy suites, usually with less cost and less hospital stay [4].

2. Background

With the widespread use of anticoagulation and antiplatelet medication, GI bleeding has become a common condition seen among gastroenterologists, and achieving effective hemostasis is paramount to successful treatment. In GI bleeding, the combination of two hemostatic modalities has demonstrated superiority over single therapy. Furthermore, failed control of bleeding during the index endoscopic procedure or re-bleeding after successful hemostasis, significantly increases the risk of mortality, emphasizing the importance in strategies to decrease this risk [5, 6].

Endoscopy has completely changed the approach to GI bleeding and has replaced surgery as the main modality of treatment. Hemostasis also constitutes one of the Halstedian principles of surgery and these principles can be extrapolated to endoscopic surgery [7].

Under normal circumstances the hemostatic process is always active and happens naturally as an interrelation between vessel contraction, platelets and coagulation factors. Hemostasis can be divided into four stages: initiation, amplification, clot formation, consolidation and dissolution, and each stage is a prospective site for a therapeutic intervention to facilitate hemostasis. Hemostasis is initiated by vessel damage, triggered by tissue factor and collagen exposure at the site of injury. The amplification process is oriented to generate thrombin through various steps. Thrombin plays a central role in the clot formation stage by promoting the conversion of fibrinogen to fibrin, which then creates a polymer that recruits platelets to form a stable clot and seal the site of vessel injury. Once the clot is formed, additional fibrin cross-linking is stimulated by factor XIIIa in order to consolidate the clot. Simultaneous to consolidation, the process of dissolution is started by a separate but interconnected system, with the conversion of plasminogen to plasmin, causing the degradation of fibrin into smaller fragments (**Figure 1**) [8, 9].

Wound healing is regulated by the interplay of cellular, humoral and molecular processes and begins after tissue damage, at the same time that the coagulation cascade is initiated. There are three phases of wound healing:

1. Inflammatory phase in which cytokines recruit pro-inflammatory cells.

2. Proliferative phase whereby fibroblasts create bands of connective tissue rich in collagen.

3. Remodeling phase, which can last for many years, and consists of the granulation tissue transforming into vigorous scar tissue [10].

Additional methods are used to expedite the process of hemostasis and achieve a stable coagulum. In a broad sense, these methods fall into three categories: thermal, mechanical or chemical [6]. Thermocoagulation coupled with irrigation and aspiration has been adapted successfully to endoscopic devices. Mechanical hemostasis in endoscopy is usually performed by using through the scope or over the scope clips, as well as detachable loops. Chemical hemostasis can be obtained from biomaterial, which are synthetic or natural substances that interact with the body, to replace tissues or augment its functions such as hemostasis and wound healing [6, 11, 12]. Biologically active materials such as thrombin and fibrin or absorbable products such as gelatins, collagen and oxidized cellulose have been used. Synthetic products and inorganic powder have also been employed in endoscopy. Besides the effects on the hemostatic process, many of these substances can have a positive or negative effect in the wound healing process [10].

Although the options for biomaterials have expanded over the last decades, the use of biomaterials to achieve chemical hemostasis has not been as widespread in endoscopy as in conventional surgery. One of the reasons is the restriction of delivering the biomaterial through the endoscope, and although most of the available options can be administered using through-the-scope injection or spraying catheters, other materials require to be grasped with endoscopic forceps and carried along the endoscope, to be delivered into the gut lumen [13–17]. The endoscopes are expensive medical equipment and endoscope damage is a genuine concern, especially with the use of acrylate polymers. It is recommended to flush the catheter immediately after acrylate use to prevent crystallization of the glue in the delivery needle. Dilution of the acrylate with lipiodol is also recommended to prevent potential clogging of the endoscopic channel [11, 18].

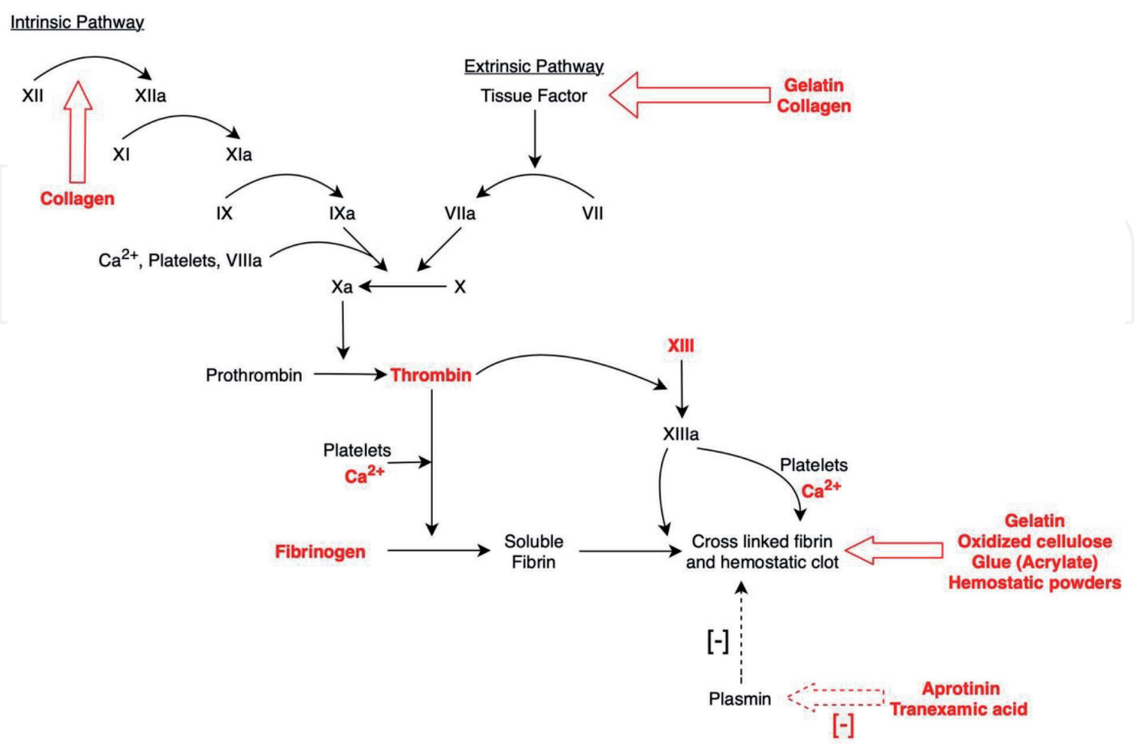

Figure 1.
Biomaterials and their effects on hemostasis.

3. Agents

3.1 Thrombin

Thrombin is an enzyme with significant roles in hemostasis, inflammation and cell signaling. It has been used since the 1940s and can be obtained from bovine, pooled human plasma and recombinant sources. It has been used routinely since the 1980s for hemostasis due to its effectiveness and ease of use [19].

Thrombin is commercially available alone and in combination with other substances, usually delivered through endoscopic needles. The injection of any agent will likely have a mechanical effect during hemostasis by compressing the bleeding vessel, also known as tamponade effect. The main effect, however, is through a complex process that releases peptides from the alpha and beta chains from fibrinogen, which in turn polymerize by hydrogen bonding in a lateral and end-to-end fashion into an unstable fibrin clot. Further stabilization occurs by covalent cross-links promoted by factor XIIIa which promotes platelet aggregation and seals the bleeding [20, 21]. Thrombin can also induce vasoconstriction and chemotaxis of neutrophils and fibroblasts as well as the production of vascular endothelial growth factor [22]. Typically, thrombin is used in combination with other drugs such as epinephrine for vasoconstriction which has demonstrated to be superior to epinephrine alone. A study was performed in 140 patients presenting with severe GI bleeding from peptic ulcers to compare epinephrine to epinephrine plus thrombin. The combination of epinephrine plus thrombin obtained permanent hemostasis more often than epinephrine alone with decreased blood transfusion requirements and significant reduction in mortality [23]. However, a similar study was performed in 64 patients which did not show any benefits from thrombin, although the dose of thrombin in this study was significantly less than the first study (150–300 IU vs. 600–1000 IU) [24]. Other studies have used a mixture of epinephrine and thrombin sprayed into the ulcer bed; however, this approach did not show any benefits [23]. The use of thrombin has also been reported in the treatment of gastric varices since 1947 [25]. Although variceal band ligation treatment is effective for bleeding from esophageal varices, the use of banding for gastric varices is limited. Gastric varices are present in 15 to 100% of patients with esophageal varices, and although less prone to bleeding, when bleeding does occur, it is often more severe with high rebleeding rates and is more challenging to achieve effective hemostasis. Currently the main modality of treatment for gastric varices is acrylate injection, however its use it typically limited to highly specialized centers given its increased risk of systemic embolization and difficulty in administration and the potential to cause damage to the endoscope. Direct injection of thrombin is another method that has been explored for the treatment of varices. This agent is most commonly delivered through endoscopic needles. Multiple series have documented its safety and efficacy achieving hemostasis in almost all patients, although no randomized trials have compared it to the other treatment modalities available [25–27]. Advances in EUS have allowed successful EUS guided thrombin injection, with theoretical less risk of systemic embolization since the feeding vessel can be identified under visualization, requiring less amounts of thrombin than direct injection with regular endoscopy [28].

3.1.1 Adverse effects

Due to its biologic nature, thrombin can be highly immunogenic and allergic reactions and autoimmune phenomena have been reported, especially with the bovine derived thrombin. Recombinant thrombin is less immunogenic than bovine

and human, but there is still a possibility of cross-reaction if a patient has had previous exposure to the other types of thrombin with resultant antibody formation [20, 22]. In regards to human thrombin, it is isolated from pooled plasma donors and there is always concern for transmission of blood-borne pathogens such as HIV and viral hepatitis as well as the theoretical risk of prion disease [29]. The use of thrombin has been associated with coagulopathy and abnormal laboratory results such as prothrombin time and partial thromboplastin time [19, 27]. The development of autoantibodies against factor V may precipitate paradoxical bleeding after thrombin injection [30, 31]. With the injection of thrombin directly into a vessel, it clots the fibrinogen of blood immediately and there is concern for distant embolization, however its use appears to be safe based on small studies [29].

3.1.2 Future directions

Currently US and European guidelines recommend acrylate injection as the initial modality of treatment for bleeding gastric varices and do not include thrombin [32, 33]. However, thrombin alone as well as in combination with gelatin matrices, has demonstrated to be effective, safe and easy to administer, contrary to sclerosing agents and acrylate. With thrombin, there is no risk of secondary bleeding from post injection ulceration, and constitutes a true alternative to acrylate [26, 28].

3.2 Fibrin

Fibrin sealant has been widely used as a tissue adhesive for non-suture closure of lesions, mimicking the last steps of the coagulation cascade where fibrinogen is converted to fibrin.

Fibrinogen is the main component in fibrin sealants and is a dimer with identical units formed by three polypeptide chains (α, β and γ) [34]. Thrombin is the only coagulation factor that can cleave fibrinogen into fibrin which then assemble into fibrils that will form a three-dimensional network. This network is further stabilized by factor XIIIa by initiating new peptide unions known as gamma-gamma dimmers to form the alpha-polymers, a process assisted by the presence of calcium. Factor XIIIa also induces crosslinking of plasmin inhibitors to protect the clot from fibrinolysis by plasmin. Once the fibrin net is formed, it attracts cells and functions as a scaffold to stimulate granulation tissue and facilitate wound healing. Fibrin also has high affinity to collagen and cell surface receptors such as integrins, which facilitate adherence to wound surfaces [21, 30, 34, 35].

The composition of multiple presentations of fibrin available in the market is variable and neither the concentration or purity of the components is uniform. Usually the product is available as a two-component kit consisting of separate fibrinogen and thrombin which acts as an activator of fibrin. Calcium is always combined with one of the components. Factor XIII, a clot stabilizer, and aprotinin or tranexamic acid acting as fibrinolysis inhibitors, are also included in the fibrinogen containing mixture. The significant variation in components of these available products affects their qualities such as viscosity, adherence force of the clot, mechanical strength, speed of clotting and resistance to proteolysis [21, 34, 36, 37].

Fibrin has been used extensively across an extensive range of surgical procedures, providing bleeding control, suture support and sealing. It has been available in Europe and Japan since the 1970s, but did not receive regulatory approval in the United States until 1998, still however, its use is not widespread in endoscopic procedures [37–39]. Most of the initial reports of the use of fibrin sealant were in the treatment of upper GI bleeding from peptic ulcer disease, delivered using injection needles in a similar fashion as thrombin. Although the studies showed conflicting

data in terms of benefits, fibrin was not shown to be superior to epinephrine injection alone [38, 40, 41]. Intravariceal injection of fibrin has also been reported for bleeding gastric varices showing efficacy to control bleeding with low risk of rebleeding [42].

Postoperative fistulas are secondary to a broad range of factors and are relatively common complications after surgery. While most fistulas respond to conservative management, healing is unlikely after 6 weeks and persistent fistulas are associated with increased morbidity and mortality from malnourishment and septic complications. Endoscopy has been used in the treatment of persistent enterocutaneous fistulas as an alternative to surgery. Fibrin application coupled with debridement of the epithelized fistulous tract and ablation of the mucosa at the internal opening has been used successfully for endoscopic sealing of the fistulous tract. Fistula occlusion intends to halt further passage of secretions, but also fibrin may have a role in stimulating wound healing by promoting fibroblast proliferation and formation of new blood vessels. Nonetheless, the studied populations are quite heterogeneous and the reported success has wide variability from 36–100% [39, 43–48]. The same technique has been used for the closure of gastrocutaneous fistulas that failed to close after gastrostomy tube removal [49].

With third space endoscopy, large amounts of tissue can be resected en-bloc using electrosurgical knives. However, bleeding and/or perforation are serious adverse event, especially in patients with resection size larger than 4 cm or taking antiplatelet or anticoagulants [16, 50]. When perforation results after ESD, the endoscopic options include endoscopic clips or suturing. The utility of clips is of limited use when dealing with large tissue defects. While suturing can close large defects, its use may be disadvantageous when the tissue is friable or the layers are thin such as in the duodenum. A new method of "tissue shielding" has been described to treat large ulcers or perforations induced by endoscopic submucosal dissection (ESD), with this technique sheets of polyglycolic acid are applied to the ESD area and then the sheet is coated with fibrin sealant. This method has demonstrated in retrospective studies, to be effective as well as simple and safe, even in patients under continued use of antiplatelets or anticoagulants, avoiding the morbidity of an emergency surgery [51–56]. The use of this technique has also demonstrated decreased risk for delayed complications such as stricture, since the defect is covered rather than closed, with results comparable or even better than with the use of systemic or intralesional injection of steroids, without the side effects associated to the use of steroids [13, 57, 58]. On the other hand, a prospective randomized study, did not show any benefit in the prevention of bleeding from the use of polyglycolic acid sheet and fibrin sealant after ESD in the stomach, in patients with high risk for bleeding [50].

A fibrin sealant spray alone has also been used during ESD for early gastric cancer, this modality of treatment was compared to standard thermal and mechanical hemostasis and showed less bleeding and earlier wound healing in the fibrin group, since micro vessels were less affected in the fibrin sealant group due to limited use of thermal coagulation [59, 60].

3.2.1 Adverse effects

Coagulopathy secondary to thrombin, which is included in the fibrin sealant has been widely documented. Aprotinin may also be present in some versions of fibrin sealants and since it is obtained from a bovine source, it includes the risk of anaphylaxis. Although aprotinin may be valuable when fibrinolysis is high, it is not considered an absolute requirement for the success of the sealant and aprotinin free versions eliminate that risk [37]. Commercially available fibrin is obtained from

multidonor blood products and HIV transmission after the use of fibrin has been reported in the past and the risk for other blood borne infections is also a theoretical risk. Presently, the available sealants in the market are virally inactivated and this risk is practically inexistent [21].

3.2.2 Future directions

Fibrin sealant is a versatile product that has multiple properties useful not only for hemostasis but also to promote wound healing, and currently is probably being underused and oftentimes misused. The ability to recreate the last stage of the coagulation mechanism allows its use as a lifesaving treatment in patients with coagulopathies. However, its use should not be limited to those patients and its use has been described more frequently during endoscopic procedures [21]. Heterologous fibrin sealants which will decrease costs and risk of blood related infections are currently under development [36].

3.3 Gelatins

Gelatin is a hemostatic agent made from hydrolyzed and purified animal collagen (swine, sheep or equine dermis or tendon). Its use in hemostasis was first reported by Correll in 1945 [61]. Capable of absorbing up to 45 times its weight of whole blood, it has become commonplace in surgery for hemostatic intervention [62]. Since its introduction, few advances in its composition have been made and is available in sponge, powder and solution forms. It has also been used in conjunction with other products that aid in hemostasis such as thrombin and tranexamic acid. Although its mechanism of action is not fully known, it is believed to act more physically than chemically, however it has been theorized that the clotting effect of gelatin sponge may be due to the release of thromboplastin from damaged platelets while coming into contact with the walls of the sponge upon entering, which then interacts with prothrombin and calcium, producing thrombin and initiating the clotting cascade [63].

It is currently indicated as a hemostatic device in surgical interventions, when control of capillary, venous, and arteriolar bleeding is not possible by conventional procedures. It has also been a basic embolic material particularly used in interventional radiology (IR) for various disease entities such as hypervascular tumors, bleeding, and preoperative embolization, showing to be quite effective. However, experience in the field of GI endoscopy is limited. In fact, most experience comes in the form of case reports. One case series describes successful EUS-guided coil injection in combination with hemostatic absorbable gelatin sponge for treatment of bleeding gastric varices [64]. In another case, IR embolization failed to achieve hemostasis in a patient with hemorrhagic shock due to an arterial hemorrhage at an oversewn bile duct stump after liver transplantation, and a gelatin slurry was applied into the bile duct stump during endoscopic retrograde cholangiopancreatography, achieving control of the bleeding [65].

Hemostatic gel matrices have been used as hemostatic agents during surgery that requires atraumatic hemostasis due to its safety and ease of use. They are composed of a flowable gelatin matrix of either bovine or swine origin and thrombin. The fluidity of the matrix offers the benefit of adapting to the shape of the wound site allowing full tissue contact. While the matrix promotes passive hemostasis from mechanical compression and platelet aggregation, the addition of thrombin will promote the coagulation process by the mechanism discussed previously, and these agents combined may also facilitate the healing process [66–68]. Since these hemostatic agents require platelet aggregation, their use is not recommended in

patients with thrombocytopenia. However, they have demonstrated efficacy even in patients with recent use of antiplatelet agents or anticoagulation. Matrices provide hemostasis in about 5 minutes and are usually absorbed from 4 to 8 weeks [68].

Like gelatins, the use of hemostatic matrices in endoscopy has been limited. Its use was extrapolated from IR procedures for varices such as coil-assisted retrograde transvenous obliteration. The reported use of matrices is mainly as adjuvant therapy with coiling during EUS guided embolization of gastric varices. The potential benefits of this absorbable material are the lack of post injection ulceration that has been associated with acrylate injection as well as the ease of administration [69, 70]. Small series have compared both modalities of treatment showing high technical and clinical success with no rebleeding after 9 months with the use of coils/hemostatic matrix, compared to rebleeding in 38% of patients in the acrylate group. There was also a decrease in the transfusion requirements and adverse events after the use of the coils/hemostatic matrix [64, 69, 70]. No intraprocedural complications were reported with the coils/hemostatic matrix, and the only minor adverse events of abdominal pain were likely related to the procedure itself [70].

One of the constraints of the fluidity of the hemostatic matrices is the need to keep the matrix in direct contact with the bleeding surface until hemostasis is achieved. Recently another concept of hemostatic matrix delivery has been reported in animals, accomplished with the use of a special applicator consisting of a nitinol mesh coated with plastic. The applicator has angular variation up to 45 degrees that allows to keep the matrix in the desired place until achieving clot formation [71].

3.3.1 Adverse effects

Although uncommon, allergic reaction to gelatins has been reported [72].

The reported adverse effects are dependent on the location and purpose of its use and include: infection, abscess formation, granuloma and compression of adjacent structures when used in a closed space [73]. Organ infarction has been reported when used for embolization [74].

3.3.2 Future directions

While the use of gelatin in hemostasis goes back to the mid 20th century, its application has certainly evolved and gained attention in the different fields of medicine, particularly surgery and intervention radiology. While there are promising case reports in the GI endoscopic literature, further studies are needed to see if this is an effective and viable option for endoscopic hemostasis.

3.4 Oxidized cellulose

Oxidized cellulose (OC) has been used clinically as a hemostatic agent since the 1940s [75, 76]. Cellulose is a polysaccharide of glucopyranose united by β-glucosidic bonds. It can be produced by two methods: using a regenerated process that forms organized fibers; and a non-regenerated process where fibers remain unorganized. Its synthesis involves multiple steps and the final product is oxidized to make it absorbable by the tissues, this process also gives its low pH to cellulose and is responsible for its hemostatic and bactericidal properties. The low pH of the physical matrix promotes platelet aggregation to form a blood clot, and the acid milieu generated by the carboxylic group cannot be survived by many gram-positive and gram-negative bacteria, including antibiotic resistant strains [76, 77]. However, this feature may be disadvantageous since the acidity makes OC cytotoxic, with detrimental effects on erythrocytes causing some hemolysis and affecting wound

healing, since acidity prevents the proliferation of fibroblast and halts the contraction of the extracellular matrix. OC also has the ability to absorb fluids and can have a tamponade effect during hemostasis [75–78]. Although non-regenerated OC may have superior hemostatic performance, the main difference between regenerated and non-regenerated OC lies in the way they are absorbed. Regenerated OC degradation starts within 18 hours of implantation via β-elimination by glycosidases and is fully absorbed in 7–14 days, while non-regenerated OC requires phagocytosis and then hydrolysis by macrophages through a longer process [10, 76, 78].

OC is used when conventional hemostasis is not effective or practical and is the chemical hemostatic agent most commonly used worldwide because it is cost-effective, easy to use, atraumatic, biocompatible, absorbable and bactericidal [10, 75, 76].

Simultaneous administration of organic hemostatics such as thrombin and/or fibrin to enhance the hemostatic properties of cellulose is purposeless since the low pH denatures the proteins and they become ineffective [76].

The use of OC in the treatment of active GI bleeding from ulcers and angiodysplasia has been reported in the literature [79, 80].

The concept of "tissue shielding" reported with the use of thrombin and a sheet of polyglycolic acid has been used with OC in animal models and recently in humans. With this technique, a fragment of hemostatic is placed over the mucosal defect to prevent bleeding after ESD has been carried out [81, 82].

Cellulose requires dry application, although a new modality of delivery has been described recently during bleeding prevention following ESD, where OC is delivered via endoscopic spraying after being mixed with saline in a syringe [15, 83].

3.4.1 Adverse effects

Although the acidity associated with the oxidized cellulose has antibacterial properties, it should be used with caution in an infected wound since the presence of a foreign body may increase the predisposition to infection or formation of granulomas [36, 73]. However, infection is probably less of a concern in the GI tract since it is not a sterile space. Due to its low pH, oxidized cellulose can either provoke a strong inflammatory reaction or delay wound healing by decreasing the number of fibroblasts, and it is recommended to remove any excess product once hemostasis is achieved [73]. There are documented reports of migration of oxidized cellulose through suture lines provoking fistulation [84].

3.4.2 Future directions

Although many of the properties of oxidized cellulose make it an attractive hemostatic product. Its use in GI endoscopy is limited to few case reports, mainly because of the constraint of delivering the product through the endoscope. And although the hemostatic effect of OC is better when applied dry, the reported use of OC by spraying has demonstrated good results and may increase its use during GI procedures.

3.5 Collagen

Collagen is a three-polypeptide chain (α-chains) characterized by the presence of one or more triple-helical domains and serves as a structural scaffold in tissue because of its stiff structure which is essential for tissue integrity. It plays an important role in hemostasis during injury, via interaction with Von Willebrand factor, integrins and clotting factors. Collagen is in the matrix underlying vascular endothelial cells. An injury will result in exposure of blood flow to subendothelial

structures that contain a high percentage of collagen which results in activation of platelets and the intrinsic coagulation pathway. Platelets bind to collagen via glycoprotein receptors, inducing a negative charged lipid to become exposed to the platelet membrane, exposing procoagulant phospholipids, leading to the change of shape reaction, triggering irreversible platelet aggregation and thrombosis. Various studies have also demonstrated administration of collagen could aid in wound healing by activation of inflammatory cells and increased vascularization of injured tissue [35, 85].

In the US, collagen-based products are being used in surgical hemostasis since the 1970s [86]. Hydrolyzed collagen is available as a viscous, amber aqueous solution or most commonly used as white hygroscopic powder. It is commercially prepared from many sources but mainly from bovine or porcine sources. Sponges incorporating collagen are manufactured by several companies to achieve hemostasis for surgical procedures, however, there is limited literature regarding the use of collagen for hemostasis during endoscopic procedures. Several case reports and small case series have demonstrated successful management of GI bleeding with use of collagen spray. A prospective study of 18 patients demonstrated collagen spray is safe and an effective hemostatic agent in treating peptic ulcers with Forrest classification category 1a and 1b. The collagen spray was used for patients that failed conventional therapy due to poor visualization or persistent bleeding after application of therapy. The collagen spray kit consists of an air pump, probe, a 7.5 Fr spray catheter, and a pre-loaded collagen cartridge containing five grams of powder. The spray catheter was passed through the working channel of the endoscope. One gram of collagen powder was delivered at a time over 10s, with the distal end of the catheter 2 to 3 cm from the lesion with maximum of 2 gram for the bleeding site. Endoscopy in this study was repeated after 24 to 48 hours, confirming treatment success [14].

Collagen injection has also been used in the treatment of a radiation induced broncho-esophageal fistula, injection in the submucosa around the fistula was performed using a standard endoscopic needle achieving closure of the fistula [87].

3.5.1 Adverse effects

Limited studies exist for GI bleeding, but extensive experience and literature is available in the field of surgery. There are no major side effects reported and potential allergic reaction is possible since most formulations are derived from bovine or porcine source.

3.5.2 Future direction

There is extensive surgical literature to support use of collagen-based products for hemostasis. Collagen spray has been successful in treating GI bleeding secondary to peptic ulcer disease, but larger studies are required to investigate this further, and also to see if its application would be beneficial in other sources of GI bleeding.

3.6 Acrylate polymers (glue)

Acrylate is a liquid monomer that can rapidly polymerize when in contact with an ionic medium like water, blood or tissue proteins. The polymer forms a strong adhesive bond to tissues with sealing properties, satisfying the definition of biomaterial. Because of the rapid polymerization, it can be combined with an ethiodized oil like Lipiodol. This combination has the advantage of prolonging the polymerization

time, controlling the speed of solidification, reducing the risk of embolization and opacifying the liquid, which allows it to be radio-opaque under fluoroscopy. However, injection of undiluted cyanoacrylate is also performed [11, 88].

Acrylate has been widely used for bleeding gastric varices and is the first line treatment for bleeding fundal varices, achieving hemostasis in more than 90% of the cases.

Studies have also demonstrated the efficacy of acrylate achieving hemostasis in refractory non-variceal GI bleed, usually after trying epinephrine injection, cauterization and/or endoscopic clips, prior to IR or surgical interventions [89–91]. Its usefulness has been demonstrated in peptic ulcer bleeding refractory to conventional hemostatic measures and also in the treatment of rectal ulcers. It has also been able to achieve hemostasis for Dieulafoy's lesion that failed hemostasis with epinephrine and bipolar cautery. Acrylate is an effective mode of treatment for bleeding ectopic varices, especially those located in the antrum as well as the duodenum, and has also demonstrated efficacy in controlling bleeding from oozing gastric vascular ectasia after argon plasma coagulation and endoscopic clips have failed. Furthermore, it has shown favorable outcomes in bleeding from tumor invasion into the intestinal wall.

Injections of acrylate are delivered endoscopically using a standard forward viewing video-endoscope via injection catheters. A 1:1 ratio of acrylate is mixed with Lipiodol and this is injected as a bolus. The tip of the endoscope and the accessory channel can be treated with silicone oil to prevent endoscopic damage, other studies have used Teflon catheters. Some studies also suggest that spraying acrylate directly over the bleeding point might be better than injection [11, 18]. A standardized injection technique was developed for the use of acrylate, performed using a Luer lock injection needle catheter. To minimize the risk of systemic embolization, it is recommended that not more than 1 mL of the acrylate/Lipiodol solution be injected into the tissue each time, multiple injections can be used but the maximum volume of each injection should be 1 mL. The dead space volume of the needle catheter should be measured and the needle should not be primed with glue before injection. A 'sandwich' technique has been described where the injecting catheter is primed with Lipiodol and Lipiodol-acrylate-Lipiodol solution is injected [92]. After injecting the glue, a second injection of distilled water is recommended, the volume of which should be the dead space volume of the needle catheter. This is done to deliver the entire glue from the catheter. When used for varices, the varix must then be probed to ensure obliteration. If the varix remains soft, another injection of 1 mL must be given [93]. Coils delivered with EUS assistance can also be used along with acrylate to provide a structure for localized acrylate polymerization [70].

3.6.1 Adverse effects

After injection, the vessel plug formed by the polymer of acrylate will be expelled from the varix as early as one week and up to a year after the procedure and rebleeding may occur [11]. Although rarely reported, the needle can get trapped in the varix due to rapid polymerization of the acrylate with inability to withdrawn the needle from the varix and/or unroofing of the varix [70]. One of the major complications of acrylate polymers is systemic embolization. Although rare, this can be potentially lethal. It is most commonly seen when acrylate is used for the treatment of isolated gastric varices type 1 [94].

Systemic embolization can lead to portal and splenic vein thrombosis, pulmonary embolism and splenic infarction. Transient bacteremia was noted in clinical studies especially in patients with advanced liver disease. Recurrent sepsis is

rare but has been reported. In patients with a patent foramen ovale, systemic embolization can lead to stroke. This can be prevented by injecting no more than 1 mL of the acrylate/Lipiodol solution. Duodenal ulcer perforation has also been described after using acrylate to control bleeding duodenal ulcers [36, 41]. Necrosis of the vessel wall with perivascular inflammation has also been described and is supposed to be related to a foreign body reaction [11].

3.6.2 Future directions

Acrylate has multiple properties that make it an efficient hemostatic agent. It is a relatively safe and easy to use agent, already established as first line treatment for gastric varices and has also demonstrated efficacy in non-variceal bleeds that are refractory to conventional methods. It can be considered prior to IR or surgical intervention for refractory GI bleeding using the above technique, especially in patients who would be poor surgical candidates. Given its inexpensive cost and ease of use, it can be considered as a second line hemostatic agent for non-variceal GI bleeding that is refractory to conventional methods.

3.7 Mineral powder

For years, inert mineral powders have been used by military medical personnel for achieving hemostasis in the field [95]. A proprietary mineral powder based on Bentonite clay has been developed and works in two different ways: as a mechanical barrier and by absorption. When in contact with the bleeding site, the powder forms a barrier over the vessel wall, quickly stopping the bleeding, and secondly, the absorbent powder increases the local concentration of clotting factors and enhances clot formation [96]. Last, it has also been postulated that the mineral powder may activate the clotting cascade along with aggregating platelets, forming a fibrin plug [97]. Given the lack of systemic absorption, the coagulum then falls off after 24–72 hours and is eliminated through the GI tract [98].

The mineral powder is available as a kit containing a hand-held device including a pressurized CO2 canister, a through-the-scope delivery catheter (10-Fr or 7-Fr), and a reservoir for the 21-g powder cartridge. The powder is delivered via push button in 1- to 2-second bursts until hemostasis is achieved. Up to three kits can be used in each patient. It has been evaluated for its safety and efficacy in numerous studies for the primary, adjunctive and rescue therapy of non-variceal gastrointestinal bleeding including: peptic ulcers, post-polypectomy bleeding, post endoscopic mucosal resection or dissection bleeding, gastric antral vascular ectasia, Dieulafoy's lesions, Mallory-Weiss tears and tumor bleeding [99].

3.7.1 Adverse effects

Rare adverse events associated to the use of the mineral powder may include embolism, intestinal obstruction, and allergic reaction to its components [100]. However, given the relatively low-pressure system used in the canister during deployment of the powder, the risk of embolism is minimal [96]. Reports of hemostatic powder dislodgement from the GI mucosa approximately 48 hours after its use may theoretically cause intestinal obstruction [98]. However, review of the literature did not reveal any of these potential adverse events. Because the mineral powder cannot be taken in by mucosal tissues, absorption and metabolism of the powder does not occur in the body, thereby nearly eliminating the risk of systemic toxicity. Since the mineral powder does not contain human or animal proteins or

botanicals and has no known allergens, it has been shown to have minimal side effects [98, 99].

3.7.2 Future directions

The advantages of the mineral powder are that, unlike traditional techniques, it is non-contact, non-thermal and does not require specific targeting making endoscopic application easier. In a summary of 19 studies comprising treatment of 234 patients with the hemostatic mineral powder, the combined rate of successful hemostasis was 88.5%. Rebleeding occurred within 72 hours in 16.2% after successful initial hemostasis [100]. Given the above, it is a welcomed addition to the endoscopic armamentarium to treat GI bleeding.

Head to head randomized controlled trials compared to more traditional hemostatic therapy (i.e. endoscopic clips, epinephrine injection, and thermal coagulation) would truly help discern the role of mineral powder in achieving endoscopic control of GI bleeding.

3.8 Polysaccharides

Another option for endoscopic hemostasis comes in the form of plant-based polysaccharide components and two such products are available currently. When the polysaccharide powder come into contact with blood it absorbs water, increasing the concentration of platelets and clotting factors, resulting in an accelerated clotting cascade. Additionally, it forms a gel-like matrix that adheres to the bleeding lesion, providing a mechanical barrier. Both available products have almost an instantaneous effect on hemostasis upon contact and since they are plant-starch derived, it is degraded and absorbed naturally by digestive enzymes within hours [101, 102].

Presently these products have been studied for endoscopic use in GI bleeding and there are case reports about successful use as salvage therapy in post-necrosectomy bleeding [17]. Current indications include upper and lower GI bleeding caused by ulcer, post polypectomy, tumor, post endoscopic mucosal dissection/ESD, in-stent, Mallory-Weiss tear, etc. [99]. It is deployed using compressed air through an endoscopic catheter. In 21 patients, the use of polysaccharide successfully achieved hemostasis in all patients when conventional therapy using dual or triple therapy had failed [101]. Another study looked at the use of polysaccharide powder in 22 patients and found to have success in 21/22 patients of which 16 patients underwent primary hemostasis with the polysaccharide [103].

3.8.1 Adverse effects

Similar to mineral powder, the side effect profile of polysaccharide based topical agents include theoretical side effects of embolism, intestinal obstruction and allergic reaction, however there are no reported cases.

3.8.2 Future directions

The use of hemostatic powders certainly has its advantages when compared to conventional modalities of endoscopic hemostasis. The hemostatic powders have been shown to be effective in upper and lower GI bleeding and as primary and salvage or bridge therapies. Polysaccharide and mineral powders have no differences when assessing short term and long-term hemostasis and rebleeding [99]. However, the majority of studies particularly looking at the polysaccharide

based topical therapies have been small and focused on adjunctive therapy. Further randomized studies are needed to assess the role of this type of hemostatic intervention.

4. Conclusion

Biomaterials have demonstrated proven efficacy and improved clinical outcomes in conventional surgery. And although the cost of these materials is higher compared to traditional hemostatics, it may be offset by the possible benefits of decreased bleeding related complications, procedure time, hospital stay and blood transfusion.

Given the advances in endoscopy over the past few decades, and healthcare leaning towards more minimally invasive first line therapies, the migration of these concepts to GI endoscopy is well positioned and likely much welcomed by endoscopists around the world. While the use of these agents has certainly expanded exponentially over the past decade, the use and prior descriptions of biomaterials in endoscopy is particularly limited, considering the full array of potential applications of these substances. Most of the reported uses of biomaterials in endoscopy are actually "off label" and more studies are required to allow for better understanding and decision-making guidance to best aid in patient care.

Conflict of interest

The authors have no financial conflicts of interest to disclose.

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