International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

Vol. 45 No. 2 July 2024, pp. 238-253

Medical Therapy of Non-Compressible Haemorrhage

Review

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Abstract – Drug delivery systems are being developed for many treatments including hemostasis. Increasing the concentration of therapeutic coagulants in areas where tissue grows and can be achieved by applying them directly to the injury, such as through catheters or external devices, or by using therapeutic methods that target the expression of molecular markers of vascular damage. Excessive bleeding is difficult to treat with external measures because blood pressure pushes hemostatic drugs out, reducing their effectiveness. This review means that small particles can be used to deliver therapeutic agents such as coagulants, small molecules, or other chemical or biological agents that enter the wounds during bleeding. A recent example of a cross-sectional study showed that stimulation increased thrombin activity and tranexamic acid in the treatment of hemorrage in 2 murine bleeding models and a porcine model of fatal non-compressible bleeding. Numerous devices are available that expose bandages and new methods that make it easier to apply them to the site of vascular injury could reduce the number of deaths from bleeding worldwide.

Keywords – Topical Hemostatic Agents, Hemostatic Products.

I. Introduction

Hemostatic transport and regulation of blood vessels by providing substances to growing hemostatic plugs and extracting substances to prevent thrombosis. The method of controlling and maintaining high concentrations of clotting factors at the site of blood loss is an important strategy for treating hemostasis and preventing hypovolemic shock and death. A number of factors have been developed that can initiate and inhibit blood vessel growth during bleeding, including biological agents such as thrombin, small molecules such as tranexamic acid (TXA), and inorganic materials such as kaolin[1-3] Application of such hemostatic agents can accelerate the production of damaged blood vessels [4]. However, basic hemostatic drugs are less effective in many clinical situations, such as when bleeding occurs from a wound, damaged blood vessels cannot be found, or wounds cannot be treated, which was the cause of deaths among young people worldwide [5]. In these cases, external agents move the material out quickly, impeding delivery and delaying the onset of wear and tear on damaged vessels. Instead, superficial clots appear on the surface of the wound, which can burst during patient transport and healing, causing rebleeding [6–8], which is associated with poor clinical outcomes [9,10]. Some intravenous agents, such as TXA and recombinant factor VIIa, are often effective, while many other anticoagulants have serious thrombotic effects when their post-injection effects are not locally enough [11–14].

1- Improving the Local Distribution of Anticoagulants

Improving the delivery of local anticoagulants to bleeding sites can improve their safety and effectiveness, and many technologies are being developed to achieve this. These include agents that mimic endogenous components of coagulation in response to biochemical signals and the presence of bleeding sites. Some of these factors, which can be soluble or particulate, bind to

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extracellular matrix factors such as collagen and plasma such as von Willebrand factor and fibrin, regulating platelet aggregation , the initiation and adhesion of the clot (13,15-18). Synthetic polymers have also been described, specifically by coagulation enzymes and coagulation mediators at the site of bleeding and thrombosis [19]. Similarly, active stimuli, such as changes in shear rate, are designed to release molecules that mediate coagulation [18,20]. For example, molecules have been produced that release fibrinolytic enzymes at the site of thrombosis in response to shear stress [20]; This method may be useful for targeted delivery of coagulant to the bleeding site. Agents that detect low shear, such as where there is a pool of hemorrhagic blood, have not been reported to our knowledge, but may also be useful [21]. Many endoscope and catheter-carrying vehicles have also been developed to improve the delivery of hemostatic agents, such as catheter-stimulating emboli agents and hemostatic sprays [22-24]. Different technologies of drug production are developed and sometimes for non-hemostatic indications and these may be useful for the treatment of bleeding on the future, such as the technologies that will be delivered to the process then activates in a controlled manner to release the healing properties [25-28]. This review focuses on one delivery vehicle in particular, the self-propelling that can be delivered to the surface of the bloodstream, which shows promise as an addition as a powerful hemostatic therapy because it delivers coagulant into wounds when applied to leaking blood. Self-propelling molecules can transport products through fluids and blood.

Several self-propelling particle systems have been developed, with applications intended for targeted drug delivery. Although few of these systems have reached in vivo testing, their diversity and intelligence make them promising self-made materials for biomedical applications [29-31]. Early reports of self-propelling microparticles use the catalytic decomposition of hydrogen peroxide to produce gas and thrust [32-34]. Since then, particles have been created using many types of stimulation, such as magnetic swimming, ultrasound motion, and bio-electrochemical reactions (30, 35-37). A variety of nanomotors have been used, including sugar, drugs, such as doxorubicin, and whole cells (29,38-41). Self-propelled nanomotors have been developed, which can be moved to the site of damage in electrical circuits, which opens up interesting prospects for the delivery of therapeutic products to wounds (42). Some reports have previously stated that pumping micromotors through biological fluids, such as blood, may be difficult, if not impossible, but this recently used a simple self-propelling particles [43-46].

2- In vivo, the drug is delivered in a self-propelling manner

Recently, the first reports have shown that self- propelling substances can work in vivo. Zinc-containing micromotors can react with stomach acid to produce gas and improve the absorption into the intestine of rats (44). We developed self- propelling substances in blood (in vivo) . The formulation uses carbonate salts, which release CO2 when mixed with solid organic acids and in contact with aqueous solutions, such as blood. For organic acids, we use TXA because it is used clinically to increase clotting during trauma by inhibiting plasmin. During the reaction, the substances dissolve, the organic acid is buffered and CO2 is produced, which dissolves a lot in the blood. The rapid production of gas allows the blood to be transported in all directions. The movement is caused by a combination of particles rising sharply, moving themselves sideways, and large-scale resulting from the release of gases. Particle stimulation significantly increased release and accumulation in lesions and local microvasculature in mice with transected tails and mice with lacerated livers. Together, our results and those of Gao et al., showed that it is possible to act as a catalyst in vivo using simple, non-catalytic, gas-producing materials without the need for external factors, such as ultrasound, or fuel sources , such as hydrogen peroxide.

3- Bleeding stops with self- propelling particles

Self- propelling carbonate is made easy to work as an effective hemostatic agent. In two mouse models, it was significantly more effective in stopping bleeding compared to non-synthetic molecules and the recombinant thrombin solution used. In a porcine model of fatal femoral artery hemorrhage, stimulation of larger thrombin molecules increased pig survival without the need to apply pressure . The ingredients are well tolerated in all animal species and there are no signs of thrombosis , local, nor systemic toxicity. These results show that self-healing molecules provide a promising vehicle to overcome transport limitations during severe bleeding and to deliver hemostatic agents to the site of vascular injury to stop bleeding. . These fractions may also be useful for the delivery of other hemostatic agents, such as TXA alone, which may be suitable for intensive care units in low-risk settings.

4. Potential applications in the treatment of bleeding and advanced delivery systems

There are many bleeding conditions that can benefit from improved delivery of hemostatic drugs. In some cases, the source of bleeding cannot be identified easily and visually, such as during endoscopic surgery or when there is a large amount of bleeding

from the cavity [47]. In these cases, it is not possible to use aids such as tension to guide the catheter or hemostatic dressing. In severe cases, bleeding is treated with hemostatic agents combined with compression, but this is not good in cases where the bleeding originates from anatomical junctions, in the abdomen , or during combat care under fire [5,48,49]. In the battlefield, unresectable bleeding accounts for the largest number of survivable deaths [50]. In severe cases with severe bleeding, catheter or intravenous therapy cannot be given at any time and patients are at risk of developing hypovolemic shock and death from exsanguination [4]. A fast-acting topical agent who provides deep healing in hard-to-reach, unresectable or profuse bleeding can reduce life-threatening bleeding. In summary, delivering treatment to the site of injury can be a major obstacle to bleeding control. A number of different technologies are currently being developed with the aim of improving the delivery of hemostatic agents to the bleeding site and overcoming transport barriers that may prevent users from having a transport or delivery system. These technologies are at various stages of discovery and validation in vivo and can address many clinical situations. Self-promotion, and its ability to move therapy up against blood flow, is one promising technology.

5- Classification of hemostatic agents

5.1. Classification by source material

Hemostatic materials can be grouped into 4 types based on the source of the material: inorganic hemostatic material, polysaccharide hemostatic material, biological hemostatic material, and synthetic hemostatic material. Hemostats are based on inorganic substances from natural minerals. They have advantages such as a large source, low cost, porous structure, exceptional absorption capacity and zero risk of blood-borne diseases, but most of them are not viable and must be removed when installed. Hemostatic substances based on polysaccharides, which are derived from natural carbohydrates, attract researchers because of their bioabsorbable properties and low cost. Biological hemostatic agents have good hemostatic efficiency by increasing the immediate coagulation factor, but the high cost and the risk of immune reactions and bacterial infections prevent the wider use of these substances. Synthetic hemostatic agents can be manufactured and formulated with other additives to improve their quality. Although the raw materials used to produce hemostatic agents are cheap, and the selection of different methods to produce synthetic hemostatic agents that work well remains the focus of research by many researchers around the world. Also, potential factors, such as cytotoxicity and lack of biodegradability, should be taken into account. Additional clinical trials are required to confirm the efficacy and safety of synthetic hemostatic agents before seeking FDA approval. Hemostatic agents are grouped into 3 groups based on their mechanism of action: hemostatic agents, procoagulants, and mucoadhesive agents. Concentrates work by absorbing water from the blood and concentrating blood components at the site of injury. Activists act by filling the blood-clotting agents that make the blood clot work. Mucoadhesive agents form a tissue barrier to blood flow through connective tissue (51).

5.2. Classification of hemostatic agents based on their main properties

5.2.1. Inorganic based hemostatic agents

Various inorganic substances have been developed to speed up blood clotting, including zeolites and clays. Hemostats are based on inorganic substances from natural minerals. They have advantages such as abundant sources, low cost, porous structure, high absorption capacity and zero risk of blood-borne diseases, but most of them are not viable and must be removed when used.

A. Zeolite

Zeolites, is a class of microporous crystalline minerals, have tetrahedral units sharing of $[SiO_4]^{4-}$ and $[AlO_4]^{5-}$. Such structures have a large surface area and high porosity materials and stimulate the hemostatic effect by absorbing water from the blood and concentrating on blood cells, platelets and factors that prevent injury , thereby promoting coagulation (52). QuikClot, the first generation zeolite hemostat, is a granular preparation that is poured directly onto the bleeding site. QuikClot quickly absorbs water, achieves hemostasis and creates an exothermic reaction, causing negative effects for in vivo applications. To avoid this side effect, the second generation QuikClot ACS (Advanced Colotting Sponge) was developed and it is said to be more effective than QuikClot, especially when it is applied to the site of a bad wound without being disturbed. This product is also easier to dispose and produces fewer exothermic reactions than QuikClot (53). Natural zeolites have other advantages over their synthetic analogues, including low cost, simple manufacturing process and high biocompatibility. In a lethal rabbit model with trauma, the hemostatic and healing properties of natural zeolite granules were evaluated. Compared to Quikclot, natural zeolite granules resulted in lower mortality (21% vs. 52.6%) and facilitated wound healing (54). To increase survival in clinical settings, a mesoporous zeolite-cotton hybrid hemostat with various advantages, such as meso-/micro-porosity, rapid blood coagulation, and

stability, is synthesized. The combination of cotton and zeolites can achieve hemostasis quickly and save life in emergencies, especially in the absence of adequate first aid measures (55).

B. Clay

Composite clay, a class of hydrated aluminum silicates, has tetrahedral silicate sheets and octahedral aluminate sheets, including 1:1 clay and 2:1 clay based on the ratio of tetrahedral leaves to octahedral sheets. Smectite is an example of a 2:1 clay mineral with an octahedral sheet between 2 tetrahedral sheets, and kaolin is an example of a 1:1 clay mineral with a tetrahedral layer of silica and an octahedral layer of aluminum. Clays improve hemostasis due to their characteristics of high surface area, significant ionic exchange and high capacity (56).

C. Smectite

WoundStat ™ (WS, TraumaCure) is a commercial smectite product consisting of smectite minerals and polyacrylic acid salts. With rapid blood flow and high cation exchange capacity, WS can concentrate platelet-derived factors at the site of injury and help facilitate the internal pathways, thus enabling hemostasis (57). Despite good hemostatic properties, the application of WS raised some safety concerns, such as the risk of thrombosis, severe inflammatory reactions, neurovascular damage and necrosis, and its use was stopped in 2009 (58). Because of its safety and efficacy, smectite is still used for the treatment of infectious diarrhea in children (59).

D. Kaolin

In addition to the absorption of the clays discussed above, the negative charge on the surface of kaolin is combined with XII, leading to the blood clotting process, which causing the eventual formation of fibrin clots (11). (QuikClot Combat Gauze™) Kheirabadi et al., evaluated the efficacy and safety of QCG, TraumaStat, Celox D, and HemCon in a porcine model of arterial bleeding and found that QCG achieved the best hemostatic effect (60). One study reported that QCG reduced blood loss and was more effective for hemostasis than standard gauze (84.6% success vs. 30.8% gauze success), with the advantages of quick use, low cost, and no side effects (61,62). As an effective and safe hemostatic agent, QCG is recommended as the first line of treatment for life-threatening bleeding on the battlefield. The QCX is similar to the QCG but has a larger mass and size. In a standard porcine haemorrhage model, the application of QCX was found to be more effective in reducing the mortality of injured animals and achieving more immediate hemostatic results than QCG, due to the increased gauze and high efficiency (63). QCTP, a sponge the size of a laptop, is designed to treat large wounds. Despite the ineffectiveness of kaolin hemostatic agents in controlling bleeding in some coagulopathic animals, QCTP combined with noninvasive wound healing has been shown to be effective in stopping fatal coagulopathic bleeding in large soft tissue wounds. (64). Furthermore, QCTP has also been used in patients undergoing surgery for spinal deformity and has been shown to be effective in reducing intraoperative blood loss and blood transfusion (65). QCI, a kaolin-coated uncoated gauze, can be used to control excessive bleeding at the injured vascular site with strict manual attachment. When applied to patients with radial artery occlusion after intervention, QCI, assisted by short-term compression, reduced the incidence of radial artery occlusion (66,67).

5.2.2 Hemostatic agent based on polysaccharides

Polysaccharides, the form of which most natural carbohydrates occur, have a branched or linear molecular structure. With their characteristics of low cost, rich properties, good compatibility and no risk of immune response, polysaccharides are well investigated as hemostatic agents, including chitosan, starch , cellulose and alginate. However, their limited hemostatic value has limited their widespread use. With the development of physical and chemical methods, a greater number of polysaccharide-based hemostatic agents have been identified.

A. Chitosan

Chitosan is the most commonly loaded polysaccharide, and the deacetylated form of chitin (the most common polysaccharide) is found in fish. Chitosan is widely used in the biomedical field due to its excellent antibacterial properties, as well as good biocompatibility and biodegradability (68). Its hemostatic effect occurs through the general activity of 3 processes: (I) Red blood cell (RBC) collection. Glucosamine is well established that chitosan can attract negatively charged red blood cells to agglutinate, thereby promoting clotting independently of the classical coagulation cascade (69); (II) Stimulation of platelets. Chitosan effectively stimulates platelet adhesion and aggregation, probably by increasing Ca 2+ concentration and promoting GPIIb/IIIa

complex expression on the platelet surface (70); (III) Changes in the structure of fibrinogen. Chitosan structures can be linked to electrostatic forces after chitosan ionization, leading to changes in the structure and function of fibrinogen (71). In addition, chitosan with different molecular weight (Mw) and degree of deacetylation (DDA) provides different hemostatic effects on the material. It is reported that chitosan should not be processed at the same Mw and DDA, but it is used as a mixed chitosan with Mw of 8.6 to 247 kDa and DDA of 75 and 88% (72).

Currently, several chitosan FDA-approved hemostatic products are commercially available, including HemCon® Bandage (HemCon Medical Technologies Inc.), Celox® (MedTrade Products Ltd.) and TraumaStat® (Ore) . HemCon® bandages use freeze-dried chitosan as a component. Due to the compression of the bandage and the hemostatic properties of chitosan, effective hemostasis is achieved in 2 minutes. However, the HemCon® dressing must be removed within 48 hours and is difficult to use for deep or small wounds due to its regidity. Celox®, which is composed of chitosan, avoids this difficulty and has a better hemostatic effect than the HemCon® dressing. In addition, Celox® is also suitable for patients with coagulation disorders. TraumaStat®, a hemostatic gauze made from silicon dioxide, chitosan and polyethylene, has a significantly larger surface area, which increases the wound contact area. TraumaStat is also more flexible and can be applied to different wound types (73).

B. Starch

Starch is a polysaccharide consisting of glucose monomers linked by α-1,4 linkages. Microporous polysaccharide hemisphere (MPH), a hydrophilic plant polysaccharide hemostatic agent, enhances the coagulation process by absorbing water from the blood and concentrating platelets and coagulation proteins (74). It has been reported that MPH can reduce seroma after mastectomy in rats, but prospective clinical studies showed no difference in the duration and rate of seroma drainage associated with the use of MPH after mastectomy (75,76). HemoStase (CryoLife, Inc.) and Arista (Medafor Inc.) are commercially available starch-based hemostatic agents. Recently, MPH, combined with mesoporous zinc-calcium silicate, has been reported to improve water absorption capacity and damage through good hemostatic and antibacterial properties (77).

C. Cellulose

Cellulose is the carbohydrate that forms the backbone of many plant structures and cells. It is the largest polysaccharide in nature and is a source of dietary fiber. Natural cellulose is insoluble in water, but oxidized cellulose (OC), an absorbable oxidation product of cellulose, may or may not result in the formation of organically regenerated cellulose (oxidized regenerated cellulose, ORC) or remain unregenerated in fiber not processed before oxidation (non-oxidized cellulose), recycled cellulose , ONRC (oxidized non-regenerated cellulose). After the oxidation process, cellulose acquires hemostatic and bactericidal properties. The low pH produced by the carboxylic acid can activate platelets to induce the formation of a temporary platelet plug. Also, it is said that the bactericidal factors are low pH, which most bacteria cannot survive. Compared to ORC, ONRC has a larger surface area due to broken fibers, antibacterial effect, and provides higher hemostatic efficiency in vivo (78). However, another study showed that the degree of oxidation and the regeneration process can affect the bacterial activity, hemostatic efficiency, and cytotoxicity of ORC and ONRC (79). Due to their ready-to-use nature, good biocompatibility, and antibacterial properties, various commercial products are obtained from modified and unmodified cellulose, such as SURGICEL®, and Traumastem (Baxter Health Care). Scientific literature has accumulated evidence supporting the efficacy and safety of the SURGICEL® family of resorbable hemostats. The SURGICEL® family includes 4 products: SURGICEL® Original, SURGICEL® Fibrillar™, SURGICEL® Snow™ and SURGICEL® Nu-knit®. SURGICEL® Original has been widely used for over 50 years with proven safety and efficacy and contains antibacterial properties. SURGICEL® Fibrillar ™ is flexible because its separated layers are easily adjustable, allowing for easy placement.

SURGICEL® Snow™ develops and provides better hemostasis and better tissue structure, control and adhesion compared to SURGICEL® Original., SURGICEL® Nu-knit® has high tensile strength and thickness, allowing it to hold sutures. The SURGICEL® family has been widely used in the field of surgery (80). Although SURGICEL products are generally safe and effective, some safety concerns have been raised when applied to clinical treatment, including delayed absorption, fiber compression and granuloma/neoplasia, among others (81). Therefore, a number of practical recommendations for the safe use of OCs, including removal as soon as hemostasis is achieved, the use of minimal amounts and conditions, and the literature in surgical reports (82) have been compiled. Halloysite [$Al_2Si_2O_5(OH)_4.2H_2O$], a naturally occurring aluminosilicate nanoclay, showed good biocompatibility and improved blood coagulation. For a better effect, combined hemostatic nanocomposite fibers (CHNF) of cellulose and halloysite is using a one-step electrospinning process. Due to the increase in

surface area and the high activity content (7 times higher clay load), CHNF helped to condense human plasma and whole blood faster than QCG (83). In addition, a recent study combined oxidized cellulose with chitosan and collagen, developing a novel hemostatic nanocomposite with satisfactory biodegradability, antibacterial properties, and anti-inflammatory properties (84).

D. Alginates

Alginate is a natural polysaccharide derived from a variety of brown algae and some types of bacteria. Its biocompatibility, low toxicity and low cost are used for many biomedical applications. It has been shown that divalent or multivalent cations, such as Ca2+, can cross the bond between soluble sodium alginate and insoluble alginate. Once calcium alginate (CA) enters the blood, Ca2+ acts as an agent to activate the clotting process. In fact, alginate does not have any hemostatic properties in the classical sense, but alginate dressings provide a physiologically soft microenvironment, prevent bacteria from the injured site, and facilitate wound healing (85,86). To improve its limited hemostasis, Pan and colleagues made microspheres containing zinc alginate (ZnAlg) and chitosan (CS@ZnAlg microspheres), which accelerate blood clotting in vitro and in vivo (87).

5.2.3 Biologically derived homeostatic materials

Biologically derived hemostatic retailers can at once boom coagulation elements at the topical damage site, prompt blood clotting, and thereby present an amazing hemostatic efficacy. these materials taking part at the end of the coagulation cascade to shape a fibrin clot are known as energetic agents, inclusive of thrombin and fibrinogen.

A. Thrombin

Thrombin, an enzyme (proteinase) in shed blood, forms from prothrombin through the action of the prothrombinase complex inside the common pathway of the coagulation cascade (88). Thrombin plays critical features in blood coagulation and platelet aggregation: (I) Direct movement with fibrinogen. As discussed above, thrombin converts fibrinogen into fibrin to shape clots; (II) oblique outcomes are mediated through different clotting elements. This impact creates a comments loop: activating the cofactors FV, FVIII, and FX to beautify its generation and activating FXIII to crosslink fibrin right into a solid plug (89,90). three assets of thrombin have been used commercially: bovine plasma (Thrombin-JMI), human pooled plasma (Evithrom), and the recombinant human thrombin (rhThrombin) (Recothrom). Animal-derived plasma, often from bovine thrombin, won't most effective lead to xenogeneic immune responses and postoperative headaches but additionally likely transmits blood-borne pathogens together with bovine spongiform encephalopathy (BSE). Even human-derived plasma can significantly reduce immunological reactions. The capacity danger of transmitting bloodborne pathogens inclusive of HIV and hepatitis B and C remains. rhThrombin has similar efficacy to animal- or human-derived plasma thrombin but has a appreciably decrease risk of an immunologic impact. In phase 3, randomized, double-blind comparative study of the efficacy and protection of rhThrombin and bovine thrombin used in surgical hemostasis, rhThrombin turned into located to motive fewer immunological reactions and had comparable efficacy and protection to bovine thrombin (91). The phase 4 rhThrombin trial's immunogenicity and protection suggested that patients with regarded preceding publicity may nonetheless be appropriately re-exposed to this topical rhThrombin (92).

B. Fibrin

Fibrin is an insoluble protein that forms a 3-dimensional protein network whilst the blood protein fibrinogen interacts with thrombin. Commercially available fibrin products named 'fibrin sealants' contain two primary components: factor one contains human-derived fibrinogen, and element carries thrombin. besides the two primary additives, different active additives normally delivered to fibrin sealants are Ca2+ and anti-fibrinolytic marketers like aprotinin (93). The hemostatic mechanisms of fibrin sealants are: (I) acting as a hemostat, fibrin sealants can growth coagulation factors in vivo and activate blood clotting; (II) acting as a sealant, fibrin sealants create a sealing barrier that bodily prevents blood loss from a structure (III) acting as an adhesive, fibrin sealants are capable of self-polymerizing and adhering systems together whilst applied in a dry discipline. whilst utilized in doubtlessly injured blood vessels, neither sealants nor adhesives possess an inherent hemostatic belongings to cause blood clotting but can be used as hemostats with the aid of gluing the injured vessel and preventing bleeding. Conclusively, fibrin sealant is the best commercially to be had FDA-accepted material for medical use in all 3 of those groups: hemostats, sealants, and adhesives (94). Several fibrin sealants are commercially available, which includes Tisseel (Baxter fitness Care), Evicel (Johnson and Johnson), Vitagel (Orthovita), Evarrest (Omrix), and ARTISS (Baxter fitness Care). Fibrin sealants had been broadly utilized in

surgical procedures to acquire hemostasis, including optionally available retroperitoneal or intraabdominal surgical treatment, non-compulsory hepatectomy, vascular surgical treatment, etc. (95-98).

Then again, no significant benefits or aspect effects have been discovered from a recent multicenter randomized managed trial to assess the impact of fibrin sealants in general knee substitute surgical operation (99). Despite those widely used hemostatic materials, positive safety issues want to be mentioned. The predominant subject relates to bloodborne diseases because of human-derived plasma. Based in this limitation, a safe, similar-efficacy and low cost recombinant human fibrin sealant (rhFS) may have an extra ability for medical use (100). In comparison to the routinely used liquid fibrin sealants, Fibrocaps (Raplixa; ProFibrix BV, a subsidiary of The drugs organisation) is a novel , dry-powder fibrin sealant used for the control of surgical bleeding. Fibrocaps, a ready-to-use powder, wishes to be stored at room temperature and may be carried out directly via a sprig tool .In spite of these extensively used hemostatic materials, sure safety issues need updated be noted. The fundamental issue relates to bloodborne diseases as a result of human-derived plasma. Based in this difficulty, a safe, similar-efficacy and low-value recombinant human fibrin sealant (rhFS) may have a greater capacity for medical use (86). In evaluation updated the up to datematically used liquid fibrin sealants, Fibrocaps (Raplixa; ProFibrix BV, a subsidiary of The medicines organization) is a unique, dry-powder fibrin sealant used for the manipulate of surgical bleeding. Fibrocaps, a ready to use powder, desires be stored at room temperature and may be implemented directly through a spray device. A latest look at indicated that Fibrocaps turned in updated powerful and safe as an adjunct up-to-date deal with moderate surgical bleeding in patients undergoing a huge sort of surgical tactics in a phase 3, global, randomized, single-blind, managed trial (101).

C. Collagen based materials

Collagen-primarily based materials encompass 3 forms of hemostatic agents: collagen, gelatin, and microfibrillar collagen. Collagen, basically found in fibrous connective tissues along with bones, skin, muscular tissues, tendons, and ligaments, serves a critical structural role in providing tensile power and flexibility for tissues and organs. Gelatin may be fashioned through thermal denaturation or irreversible hydrolysis of collagen, and microfibrillar collagen is a new bodily shape of collagen, which is derived via converting bovine collagen right into a partial hydrochloric acid amine salt of bovine collagen (102,103) , at least 29 sorts of collagen had been identified and categorised typically updated their systems, with over 90% of those inside the body categorised as type I. The remarkable characteristics of collagen include smooth extractability, low cost, and desirable biocompatibility, which make collagen an appealing biomaterial for developing medical merchandise and therapeutic gadgets (103). The roles of collagen in thrombosis and hemostasis are as follows: (I) indirect outcomes mediated via platelets. while blood vessels intact, blood will waft smoothly over the subendothelial structures constituting the connective tissue which includes a high percentage of collagen. once uncovered updated blood drift, collagen gives the matrix structure for platelet adhesion, aggregation, and activation; (II) direct interplay with clotting elements. Collagen turns on the intrinsic pathway of the coagulation cascade via three clotting factor: the activation of factor XII, the binding of factor IX to collagen type IV, and the interplay with the von Willebrand factor (vWF) (104). As compared up to date OC patches, collagen-based patches have more reliable mechanical residences and may lessen swelling and adhesion formation inside the frame (105). Arepresentative, commercially availableupdated collagen product is Stypro® hemostatic sponge (Curasan AG), derived from bovine collagen.

The microporous and inter-connective shape of the sponge stimulates the coagulation cascade through its up-to-date absorption ability (as much as 50 instances its weight). another commercially up-to-date collagen product is HEMOBLAST™ Bellows (Biom'up), that's a powder composed of porcine-derived collagen, bovine-derived chondroitin sulfate, and human-derived thrombin. The powder has numerous incredible traits, inclusive of biocompatibility and reabsorption inside 4 weeks, and it is straightforward and equipped up to use (106). Oxidized microcrystalline cellulose (OMCC), a new type of oxidized regenerated cellulose, is regarded as an inexpensive and effective hemostat biological safety, low price, and an excellent hemostatic impact. these days, researchers have fabricated a composite containing single-collagen sponges and OMCC hemostatic capability of collagen. The consequences showed that the composite reduced the lengths of the activated partial thromboplastin time (APTT) and thrombin time (TT) in vitro, and supplied a speedy hemostatic impact in vivo (107). Commercially collagen-based agents, commonly derived from bovine and swine, deliver the capability chance of transmitting illnesses which include BSE and transmissible spongiform encephalopathy (TSE), and porcine collagen can also give religious objections in certain cultures. Based on those inevitable issues, jellyfish collagen become extracted from Rhopilema esculentum Kishinouye (R. esculentum), that's one of the maximum ample species of jellyfish in China. due to their porous structure and better water absorption rate, jellyfish collagen sponges exhibited speedy hemostasis and a more decrease in the amount of blood loss than medical gauze (108).

D. Gelatin

Gelatin, organized from purified red meat skin gelatin or bovine-derived gelatin, is available in sponge, powder, or granular forms and may be absorbed inside 4 to 6 weeks. Compared with animal-derived fibrin or collagen, gelatin is superior in its biocompatibility, biodegradability, and occasional immunogenicity. Gelatin substances now not only effective soak up over their weight of blood but also concentrating clotting factors and platelets at the site of damage. After absorbing water, gelatin material swells, which in turn gives a compressive impact on the wound site. moreover, gelatin can offer a structural matrix for clotting (109). To improve gelatin's thermal and mechanical balance, a chemical crosslinker may be used to react with the amine groups in gelatin, amongst which glutaraldehyde (GLA) is the maximum broadly used and comparatively less expensive crosslinker. it's been established that gelatin sponges containing 1% w/v gelatin and 0.5% w/v glutaraldehyde had accurate mechanical energy, progressed water absorption capability, and hemostatic effectiveness with none risk of toxicity (110). Currently, there are several commercially gelatin-primarily based products, such as GelFoam (Pfizer), FloSeal (Baxter fitness Care), and Surgiflo (Johnson and Johnson). GelFoam, a stable gelatin-primarily based product, can swell as much as twice its length after soaking up water from the blood, which affords a tamponade impact to site of bleeding. however, the tamponade impact may additionally purpose compression-related aspect effects, which include compression of nerves in the spinal cord (111). FloSeal, a liquid gelatin product, carries a proprietary blend of a gelatin matrix and thrombin and is ready via mixing them straight away earlier than use. FloSeal has an extensive variety of scientific applications no longer best due to its benefit of a tamponade effect but additionally its liquid shape lets in flexibility in its applications to irregular wounds, ensuing in intimate contact of FloSeal with the site of bleeding. moreover, FloSeal may be adequately used in restrained surgical areas, in which high concentrations of thrombin achieve effective hemostasis (112).These days, because of their controllable morphology and surface properties, nanofibrous substances have had a wide variety of packages in biomedical regions, as wound dressing, drug delivery, tissue engineering, and hemostasis (113). Xie et al., fabricated an injectable and elastic nanofiber rectangle matrix (“peanut”) coated with gelatin. They tested that the “peanut” presented effective hemostasis in a porcine liver by means of soaking up water and accelerating the clotting procedures (114).

D. Microfibrillar collagen

Microfibrillar collagen, crafted from purified bovine collagen and carried out in a dry, free flour form, is one of the most extensively used to topical hemostatic agents. Microfibrillar collagen can be applied to wet environments inclusive bleeding wounds. however, the need for gloves or surgical instruments in its use limits its application. Several special products are inclusive of Avitene, Avitene Flour, EndoAvitene, Avitene Ultrafoam, Avitene UltraWrap (Davol), Instat (Johnson and Johnson), Helitene (Integra), and Helistat(Integra). A single-middle, randomized clinical trial evaluating the hemostatic effectiveness of microfibrillar collagen and OC in arterial bypass surgical treatment has shown that microfibrillar collagen stopped suture hole bleedings significantly faster than oxidized cellulose (115).

E. Bovine albumin

Gelatin–resorcinol–formaldehyde–glutaraldehyde (GRFG) glue, also called "French glue", comprises a formaldehyde/glutaraldehyde aggregate and a solution of gelatin, resorcinol, and calcium chloride. GRFG bonds to tissue covalently and tightly, but the same biochemical reactions might also deliver toxicity, tissue necrosis, and different overdue headaches. even though GRFG has been broadly used in Europe and Asia, it has not yet been authorised by means of the FDA for clinical use inside the USA, in particular due updated its side effects results, which includes the high concentrations of formaldehyde-related tissue toxicity. BioGlue, composed of 45% purified bovine serum albumin (BSA) and 10% glutaraldehyde, has been accepted by means of the FDA to be used as a tissue adhesive, normally implemented earlier than perfusion (116). Without formaldehyde in its ingredient, BioGlue is thought purpose much less toxicity. whilst implemented, it creates a mechanical sealant by means of bonding the tissue proteins on the injury site. But, it works in a bloodless and dry field. Therefore, BioGlue is usually used as an adjunct following closure of huge blood vessels, but not used to- active bleeding. Even though BioGlue affords a good mechanical barrier and reasons less toxicity, it still consists of the capability hazard of tissue harm, mass effect, and embolic headaches (117).Whey protein, comprised specially of β-lactoglobulin, α-lactalbumin, and BSA can be used as a protein polymer to react with glutaraldehyde. Researchers fabricated a unique tissue adhesive by using changed BSA with whey protein, because of the abundant source and low cost of whey protein. The outcomes showed that this novel adhesive presented a similar adhesive strength compared to BioGlue® (118).

5.2.4. Synthetically derived hemostatic materials

Synthetic hemostatic materials are any other type of hemostatic material that can be produced industrially and can be formulated with other adjuncts to their biocompatibility, balance, and clinical overall performance. however, the toxicity and non-biodegradability of artificial hemostatic substances are potential problems, which should be stated in future development efforts.

A. Polyethylene glycol

Polyethylene glycol (PEG), is a multi-arm copolymer with an N-hydroxysuccinimide (NHS) ester at each quit. up to updated its outstanding biocompatibility, excessive water absorption, ease of binding with biomolecules(119), and more than one gelation mechanisms, PEG is extensively used in the formation of hydrogels. PEG-primarily based tissue sealants have been considerably studied in the treatment of air leakage, acute aortic dissection, and suture hole bleeding worried in special surgical tactics (119). currently, PEG-based updated tissue sealants are updated. CoSeal (Baxter health Care), an FDA-authorized sealant, has been used for some urologic strategies, even as Duraseal (Covidien) is indicated for dural sealing (120).

several PEG-up-to-date hydrogel adhesives were synthesized and studied currently. specially, three hydrogels with one of a kind quantities of Schiff-base moieties from 4-arm-PEG-NH2, 4-arm-PEG-NHS, and 4-arm-PEG-CHO had been constructed. 4-arm-PEG became selected to construct nicely-described hydrogel networks that yield excessive mechanical strength, even as Schiff base pass-links can optimize the energy and antibacterial results. As a result, the synthesized hydrogels exhibited porous systems, splendid mechanical strength, a high swelling ratio, and antibacterial outcomes, which might be favourable for haemostasis in critical conditions (121). PEG-up to dated adhesives regularly require irradiation polymerize their components, which is impractical for lots organs of the body and limits their application in emergencies.

B. Cyanoacrylate

Cyanoacrylate monomers, in low-viscosity liquid form, are synthesized by means of the condensation of cyanoacetate and formaldehyde in conditions of warmth and a vacuum. Whilst with various anionic materials, along with blood, the basic cyanoacrylate monomer polymerizes in long chains forming the adhesive film that glues the wound and holds the apposed edges collectively together. The adhesive does no longer need to be removed after use for the reason that adhesive substance usually sloughs off within 5 to 10 days as the epidermis regenerates (122). In spite of imparting a hemostatic impact on application, cyanoacrylate adhesives do no longer possess inherent hemostatic properties causing blood clotting, but instead block holes in the vessel to prevent bleeding. Cyanoacrylate topical adhesives are endorsed for sealing low-tension wounds that are easy and dry however cannot be used on excessive-tension wounds. The cyanoacrylate alkyl side chain's period and complexity can at once have an effect on their mechanical strength and other physical properties. Quick, straight-chain derivatives (ethyl or butyl cyanoacrylate) are advanced long-chain derivatives (octyl-cyanoacrylate) in terms of forming tighter and stronger bonds, at the same time As lengthy-chain derivatives have much less side effects and reduce infection (123). There are currently FDA-accepted cyanoacrylate sealants, 2-octyl cyanoacrylate (advertised as Dermabond with the aid of Johnson and Johnson), and butyl-2-cyanoacrylate, (marketed as Hisup, Braun), which can be limited to skin closure use. Clinically, ethyl-2-cyanoacrylate is cost-powerful, time-saving, and successful in repair satisfaction when used in a children's emergency department (124). Moreover, octyl-2-cyanoacrylate has been used efficiently for cleft lip closure with the advantages of a particularly quick and painless technique, with much less chance of tissue response and wound infection (125). However, the opportunity of cell toxicity, foreign body reaction, and occasional tensile strength should be noted (126). In general, this evaluate in short summarizes hemostatic materials in phrases in their structure, mechanisms of actions, advantages, and downsides, commercially updated products and their applications, in addition updated recent traits. moreover, numerous promising products display superb potential in medical use, and ongoing clinical trials are being performed to discover their safety and efficacy in distinct areas .

6. Future outlook

Enhanced hemostatic materials possess significant promise for clinical utilization, yet only a limited number have transitioned from experimental investigations to practical clinical implementations. It is widely recognized that developing innovative products and consistently refining their hemostatic characteristics play a crucial role in managing hemorrhage and diminishing fatality rates. Thus, forthcoming studies need to integrate diverse materials and technologies to pinpoint an optimal hemostatic solution. To enhance the hemostatic effectiveness, it is imperative to develop composite hemostatic materials that incorporate multiple active agents, given the constrained hemostatic capabilities of single-component materials. Enhancing the efficacy of hemostatic products through modern technology is imperative. Besides demonstrating superior hemostatic abilities, products could achieve broader utilization by incorporating supplementary benefits such as antibacterial, anti-inflammatory, and accelerated wound healing attributes. Additionally, there is a need to create hemostatic materials and products tailored to specific types of tissues. These innovative hemostatic solutions should be designed to address various characteristics of tissue wounds, including their shapes and depths. Lastly, extensive cross-disciplinary research endeavours are essential to carry out comprehensive investigations for developing an optimal hemostatic dressing. This includes creating and refining trauma animal models, innovating efficient hemostatic tools, and executing clinical trials in diverse collaborative environments.

Conflict of Interest

All authors declare no conflicts of interest.

Author Contribution

Authors ave equally participated and shared every item of the work.

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