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Classifying the hemostatic armamentarium of the surgeon

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ABSTRACT

Hemorrhage can result in an increased mortality and morbidity. There are a variety of options to assist the surgeon in achieving hemostasis. Modalities that result, or assist, in hemostasis were included under the term Hemostatic Modalities. Due to the variety of hemostatic modalities available, choosing the correct modality tailored for each situation and patient can be confusing. The aim was to classify and organize the different hemostatic modalities in the armamentarium available to the surgeon. Hemostatic modalities can be classified into systemic and local modalities. Systemic hemostatic modalities include blood component therapy and anticoagulant antidotes. Local hemostatic modalities are subdivided into vasoconstrictors, electrical devices, mechanical modalities, endovascular modalities and topical hemostatic agents. Topical hemostatic agents can be further subclassified into agents that function with an intact or dysfunctional patient coagulation system, i.e. "independent of the coagulation system", and those that only function with an intact patient coagulation system, i.e. "dependent on the coagulation system". Classifying hemostatic modalities allows for a more informed decision and a structured approach when choosing the appropriate modality. The different classes, as well as within the classes, are by no means isolated and can be used concurrently, depending on the situation, resulting in a synergistic effect for hemostasis.

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Introduction

Hemorrhage can result in an increased mortality and morbidity. Blood transfusion also increases the risk of blood related reactions and transmitted infections. Hemorrhagic control is therefore of crucial importance. There are a variety of options to assist the surgeon in achieving hemostasis. There are also multiple factors to consider when deciding which hemostatic modality is required in a bleeding patient. Quantifying surgical bleeding assists in determining the treatment chosen for hemostatic control.

Determining the probability of bleeding in an emergency trauma related situation can be predicted with multiple scoring systems, such as the Shock Index (SI),(1) Pulse Rate Over Pressure Evaluation (ROPE) score(2) and Trauma Associated Severe Hemorrhage (TASH) score (3).

Bleeding assessment for elective procedures can be predicted with the Validated intraoperative bleeding scale (VIBe Scale) and Spot grade (4,5). The type of hemostatic modality may also be determined by the condition of the patient, i.e. coagulopathic versus non-coagulopathic, and location of the bleed. Modalities that result, or assist, in hemostasis were included under the term Hemostatic Modalities.

Due to the variety of hemostatic modalities available, choosing the correct modality tailored for each situation and patient can be confusing. The aim was to classify and organize the different hemostatic modalities in the armamentarium available to the surgeon (Figure 1).

The different classes, as well as within the classes, are by no means isolated and can be used concurrently depending on the situation.

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Figure 1: Classification of hemostatic modalities

Literature Review

Systemic Hemostatic Modalities

Although blood products, such as whole blood and fresh frozen plasma, are an integral part of resuscitation, they can also be considered part of hemostatic therapy. Hemorrhage requiring massive transfusion can result in coagulopathy. Trauma-induced coagulopathy is a typical example resulting from hypoperfusion, tissue injury, dilution and consumption of platelet and clotting factors (6).

A vicious cycle of hemorrhage and coagulopathy occurs. In addition to controlling the surgical bleed, systemic hemostatic agents such as platelets (7) and clotting factors may be required. Platelets can be transfused therapeutically to control hemorrhage or prophylactically to decrease risk of hemorrhage (8). Multiple clotting factors may be transfused in the form of fresh frozen plasma or cryoprecipitate. Fresh frozen plasma contains all the clotting factors including the physiological anticoagulants, such as protein C and protein S (9). Cryoprecipitate contains fibrinogen, von Willebrand factor and factor VIII (10). Fibrinogen is typically the first clotting factor to decrease in major.

hemorrhage which has been observed in patients that have lost more than 20% of their blood volume in major elective abdominal surgery (11). The basis for cryoprecipitate transfusion is to provide fibrinogen. Although FFP offers fibrinogen, the concentration is lower in FFP, which contains 400-900mg in 200-250ml (1 unit bag), compared to cryoprecipitate, which contains 2500mg in 150ml (10 unit

bag)(12). Fibrinogen concentrate is also available for congenital or acquired fibrinogen deficiency.10 Individual specific coagulation factors are available and may be required for certain disorders, such as hemophilia.10 Determining which systemic hemostatic agents are required in a bleeding patient can be facilitated by the "goal-directed" approach with functional viscoelastic testing (13).

Tranexamic acid, an antifibrinolytic hemostatic agent, has been advocated for severe hemorrhage in trauma patients and for post-partem hemorrhage (14). Tranexamic acid has been shown to prevent hyperfibrinolysis in trauma patients if started within three hours of injury.14 Besides systemic therapy, tranexamic acid can also be applied locally in dressings for wound hemostasis (15).

Antidotes, or reversal agents, for bleeding patients on anticoagulation medication may also be broadly considered as systemic hemostatic agents. Protamine sulfate reverses antithrombin III activator heparin; vitamin K and four-factor prothrombin complex concentrate reverses vitamin K antagonist warfarin (16); andexanet alpha is the antidote for direct factor Xa inhibitors apixaban and rivaroxaban (17); and idarucizumab is the antidote for direct thrombin inhibitor dabigatran (18).

Local Hemostatic Modalities

Vasoconstrictors

Vasoconstrictors, such as epinephrine, functions by non-selectively activating adrenoreceptors. Epinephrine is commonly mixed with local anaesthetics for cutaneous procedures (15). Epinephrine is also used in endoscopic procedures for its hemostatic vasoconstrictive effect to control hemorrhage from peptic ulcers (19). Epinephrine can also be applied directly to a wound base in the form of a gauze soaked with epinephrine (20).

Local topical application of cocaine also results in vasoconstriction. However, the use of cocaine has to be applied with caution as there are risk of complications, such as tachycardia, stroke and cardiac arrhythmias (15).

Energy Devices

Energy devices are in the form of electrical or ultrasonic devices and can be used for open or laparoscopic surgery. Electrosurgical devices uses thermal effect to obtain hemostasis. Monopolar electrocautery has the ability to seal vessels that are 1-2mm in diameter (21). Conventional bipolar electrosurgical instruments seals the vessels by denaturing the vessel wall proteins as current is passed through the tissues between the electrodes (21). Bipolar electric devices have advanced by incorporating a computer controlled tissue feedback system, pulsatile electrical energy flow and a cutting mechanism to decrease damage to the surrounding tissues (21). Advanced bipolar computer-controlled electrosurgical devices are effective for hemostasis of vessels up to 7mm in diameter and is an alternative to traditional ligation of vessels (22). These energy devices have improved operative hemostasis in multiple types of surgery, including thyroid, colorectal, gynecological and urological surgery.22-24 The advanced bipolar devices allows for easier vessel control in a limited operating field. The thermal damage to the surrounding tissues can occur 1-6mm from the jaws of the device (21). Ultrasonic devices generate heat by mechanical vibrations instead of electrosurgical current. Ultrasonic devices are able to seal and cut vessels up to 5mm in diameter due to the protein denaturation and coagulum formation (25).

Hybrid devices, on the other hand, combine electrosurgical and ultrasonic generated heat simultaneously. Hybrid devices are able to seal vessels up to 7mm in diameter (26). Thermal damage for both the ultrasonic and hybrid devices can occur up to 5mm to the surrounding tissues (26). Endoscopic management of bleeding peptic ulcers also utilizes electrical thermal devices such as bipolar electrocoagulation and heater probes, both of which require contact with the bleeding surface (27). Argon plasma coagulation is a noncontact device which can be used in a variety of surgical procedures including endoscopic hemostasis. Argon plasma coagulation is a monopolar noncontact electrocautery that uses an electrical current to ionize the argon gas flow resulting in coagulation (28).

Mechanical

Tying off a bleeding vessel with sutures is the traditional method for hemostasis, however surgical clips are commonly use due to the practicality in application in areas with difficult exposure and the decreased time for application. Clips applied to a vessel are an effective hemostatic method and do not cause as much tissue injury compared to thermal methods (27). Clips can be used in a variety of procedures, including laparoscopic and endoscopic surgery. Endoscopic clips can be applied for bleeding ulcers or bleeding diverticular disease. Other endoscopic hemostatic modalities, specifically to control bleeding oesophageal varices, include self-expandable metal stents and rubber band ligation (29,30).

Endoscopic variceal banding is performed by suctioning the varix toward the endoscope tip and a rubber band is discharged around the base of the varix. However, a rubber band may fall off if there is fibrosis of the mucosa (29).

Some hemostatic mechanical modalities can be considered as temporary, such as pressure packing, Foley catheters in penetrating wound, vascular shunts, Sengstaken-Blakemore tubes and pelvic

binders. Temporary mechanical modalities may be appropriate for hemodynamically unstable patients thereby allowing time for resuscitation and followed by definitive treatment. Sengstaken-Blakemore tubes are common endoscopic modality for bleeding oesophageal, or gastric varices, and are effective in 80% of patients (29).

However, the tube should not be used longer than 24 hours due the risk of pressure necrosis of the oesophagus. Pelvic binders are temporizing modalities for exsanguinating hemorrhage from severe pelvic fractures in order to temporarily maintain pelvic stability. Pelvic binders also have risks of complications, including soft tissue pressure sores and necrosis, especially over bony prominences, and further displacement of a lateral compression fracture (31).

Endovascular

Resuscitative endovascular balloon occlusion of the aorta (REBOA) is another method for temporary hemostasis. REBOA can be used for exsanguinating torso hemorrhage especially in patients with pelvic fractures.32 REBOA can have complications of distal ischemia and acute reperfusion injury after deflation when used for a prolonged period (33).

Endovascular stenting and embolization are two definitive intravascular hemostatic modalities. Embolization is utilized mostly for bleeding small vessels, which can be sacrificed, and for pseudoaneurysms; whereas stenting is mostly utilized for large vessels (34). Interventional radiology with transarterial embolization (TAE) has been demonstrated to be an effective hemostatic modality for the control of arterial hemorrhage, especially for abdominopelvic trauma (35). 36 Hemostatic control with TAE in a trauma patient should be considered as urgent as operative interventions since a delay more than one hour doubles the mortality risk (36).

Technical and clinical success of TAE is up to 98.9% and 91.75% respectively. Rebleeding rate can occur even with successful embolization and ranges from 6.38% to 25.6%.35 TAE can also be used in the control of non-trauma related hemorrhage, such as bleeding peptic ulcers after failed endoscopic intervention, as an alternative to open surgery (37).

TAE embolic agents include gelfoam, coils, polyvinyl alcohol (PVA), gelatin particles and N-butyl-Cyanoacrylate (especially when damage control is required) (35,38). TAE is not without risks though, complications can be divided into arterial access site (e.g. arteriovenous fistula, arterial access hematoma, pseudoaneurysm), target artery (e.g. vessel rupture and dissection) and effects of embolization (e.g. necrosis and infarction)(35).

Endovascular stenting is commonly used for arterial bleeds but can also be used for inferior vena cava bleeding (39). Hemorrhagic conditions indicated for endovascular stenting include aneurysms, arterio-enteric fistulas (40) and traumatic vascular injuries (41,420.) Endovascular aortic repair (EVAR), and thoracic endovascular aortic repair (TEVAR), are used for ruptured aortic aneurysms. Compared to open surgery, TEVAR has a better survival rate at 4 years of 75.2% (compared to 64.3% for open surgery) and avoids a thoracotomy. EVAR has also shown to have a better mortality and morbidity compared to open surgery whether the patient is stable or unstable (43). Endovascular stenting is minimally invasive, avoids aortic cross-clamping, reduces operating time and reduced blood loss (44). However, endovascular stenting also has potential complications including endoleaks, arterial access injury, ischemic complications and infection of the stent (45).

Topical hemostatic agents

Topical hemostatic modalities, usually referred to as topical hemostatic agents, have been documented since 1886 (46). Multiple hemostatic agents have since been introduced with matrices containing various bioactive ingredients. The ideal hemostatic agent requires the qualities of safety, efficacy, sustained hemostasis, cost-effectiveness, practicality, easy administration and biocompatibility (47-49).

There is currently no universal hemostatic dressing (50). Topical hemostatic agents are commonly produced as a dressing but may be produced in different forms such as foams, powders or gels depending on the indication and location for application such as deep and intra-cavitatory wounds.49 Tompeck et al. has summarized the indications of topical hemostatic agents for specific types of surgical procedures (49).

Topical hemostatic modalities can be appropriately classified into agents that function with an intact or dysfunctional patient coagulation system, i.e. “independent of the coagulation system”, and those that only function with an intact patient coagulation system, i.e. “dependent on the coagulation system”. From these two categories, topical hemostatic agents can then be subclassified, according to the traditional classification, by mechanism of action, i.e. mechanical, active, flowable, fibrin sealents and chemical agents (51).

Dependent on the coagulation system

Topical hemostatic agents that are dependent of the patient’s coagulation system include mechanical and chemical agents. These hemostatic agents require functional platelets and an intact coagulation cascade. Mechanical agents can be further subclassified into physical, porcine gelatin and oxidized cellulose-based agents. Physical agents, such as bone wax, acts by tamponing bleeding from bone edges (52).

Porcine gelatin and oxidized cellulose-based agents are hydophilic and absorb blood which provides a matrix for platelet adherence, platelet activation and concentrating coagulation factors (52,53).

Oxidized cellulose-based products have an acidic nature which has a bacteriostatic advantage but also has a disadvantage of inactivating concomitant hemostatic agents (54). Typical chemical agents such as kaolin (a soft white clay) and zeolite (derived from lava rock) contains aluminium silicate. Aluminium silicate absorbs water resulting in an accumulation of platelets and clotting factors in the wound, as well as, activating clotting factor XII. A disadvantage is the exothermic action produced which can cause localized burns (52). Quick clot combat gauze is a typical aluminium silicate hemostatic agent and has been recommended for non-coagulopathic compressible bleeding in the pre-hospital setting (55).

Independent of the coagulation system

Topical hemostatic agents that are independent of the patient's coagulation system include mechanical, active, flowable, fibrin sealents and chemical agents. Mechanical agents, including bovine collagen and polysaccharide hemospheres, have similar functioning to porcine gelatin and oxidized cellulose-based agents, i.e. hydophilic and absorb blood. However, bovine collagen and polysaccharide hemostatic agents have been reported to function regardless if patients are on anticoagulation medication (15,20).

Polysaccharide based dressings, such as chitin, also causes endothelial release of vasoactive components causing vasoconstriction, platelet activation and red blood cell accumulation in the wound (53). Active agents are independent of the patient's coagulation system as they donate thrombin to the bleeding site. Thrombin can be derived from pooled human plasma, bovine or recombinant technology. Active agents are more appropriate for patients that are on antiplatelet or anticoagulation therapy as the efficacy is still maintained (52).

Flowable agents combine the advantages of mechanical and active agents. The mechanical component uses cross-linked bovine gelatin particles which creates a tamponade effect and provides a matrix for platelet and coagulation accumulation (52). Thrombin constitutes the active component. Gelatin and thrombin are mixed in a blending applicator and delivered into the bleeding site resulting in a stable clot (52).

Sealant do not use the patient's coagulation factors and therefore function regardless of coagulation status.53 Sealants can be composed of either fibrin, albumen with glutaraldehyde, polyethylene gycol (PEG) polymer or cyanoacrylate. Fibrin sealants are derived from pooled plasma and contain factor XIII, or an antifibrinolytic agent, thrombin and fibrinogen, which activates on application of the dressing to the wound. Fibrin sealants are biodegradable and therefore do not have to be removed. Although there is a high concentration of fibrinogen delivered, there is a risk of bloodborne pathogen transmission (49). Some sealents also contain platelets which provides multiple growth factors when activated thereby improving clot strength (56). Albumin with glutaraldehyde sealants consists of bovine albumin which fuse with the wound cell proteins to form a matrix that adheres to tissue or a synthetic graft. The mechanism of action is by denaturation of albumin. This agent is suitable for large vessel arterial repair with anastomosis or synthetic grafts (53).

On-the-other-hand, PEG polymers are synthetic and therefore do not contain human or animal components decreasing risk of bloodborne pathogen transmissions (57). PEG polymers, in the form of a hydrogel, cross-links with proteins in the wound to form a cohesive barrier to blood. Cyanoacrylates, a synthetic sealant liquid, can also be used for vascular anastomosis, but the primary indication is for wound closure. However, cyanoacrylates can be neurotoxic and have been known to cause inflammatory reactions (20). Chemical agent, such as zinc paste or aluminum chloride, cause tissue destruction which results in precipitation of proteins, vessel occlusion and coagulation (52). As a result of the tissue destruction, the area of application may have local irritation and pain. Dressings soaked in vasoconstricting hemostatic modalities such as epinephrine, results in vasoconstriction of small vessels around the wound. Tranexamic acid may also be added to dressings to prevent the breakdown of fibrin network (52).

Advancements in hemostatic agents

Newer technology and advancements in hemostatic agents are under development. Nanofibers, generated from self-assembling peptides, allow for blood components to be activated. The nanofiber diameter can be changed to alter the surface to volume ratio. The fibers can be created with a combination of synthetic and natural products in order to create nanofibers with the desired mechanical properties (50). Clot-augmenting biotherapeutics in the form of intravenous nanoparticles could potentially contain elements for coagulation. The nanoparticle would allow for targeted drug delivery of hemostatic agents which can be achieved by using the patient's own platelets, or red blood cells, as a delivery method. The drug could be contained in a polyelectrolyte multilayer capsule which will protect the drug from the patient's anticoagulation system (58,59,60).

Iron oxide and silica nanoparticles have also shown promise for wound closure with resulting

hemostasis. The nanoparticles in droplet form are delivered into a wound which are absorbed into the tissue edges. With manual pressure, the nanoparticles promote linking of the wound edges and induce hemostasis after one minute (61). Nanoparticles, in the form of liposomes, could mimic platelet adhesion and platelet aggregation. The surface of liposomes can be covered with collagen and von Willebrand factor-binding peptides resulting in high adhesion to the wound causing hemostasis (62).

Combining different hemostatic properties from different classes of hemostatic agents allows for a synergistic effect thereby improving hemostasis. Combining chitosan and kaolin in the form of porous microspheres have shown an improved efficacy in animal models (63). Hemostatic microspheres have the independent mechanical hemostasic effects of chitosan with the dependent physiological hemostatic effects of kaolin. Chitosan with kaolin has been shown to decrease bleeding time by 63 seconds in rat amputation models and 35 seconds in rat liver laceration models (63).

The combination of an antifibrinolytic hemostatic modality, tranexamic acid, with a physical hemostatic agent, cross-linked microporous starch (polysaccharide agent), has also demonstated a 70% shorter clotting time (64). Hemoblast, is another combined agent composed of multiple hemostatic agents, i.e. human-derived thrombin, bovine chondroitin sulfate and porcine collagen. Compared to other individual agents in a randomized control multicenter clinical trial, Hemoblast was shown to be non-inferior ($P<0.0001$) and demonstated superiority ($P<0.0001$), with quicker time to achieve hemostasis (65). Combining hemostatic properties into a single hemostatic agent therefore appears to increase versatility of the agent.

Conclusion

There are various hemostatic modalities available to the surgeon. The type of modality chosen is influenced by multiple factors including location of the bleed, patient coagulation status, quantity of bleeding and the cause of the bleed. Classifying hemostatic modalities allows for a more informed decision and a structured approach when choosing the appropriate modality. A variety of hemostatic modalities from different classes, or within the same class, may be appropriate concurrently resulting in a synergistic effect for hemostasis.

Conflict of interest

Authors declare that have no competing interest.

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