58

Topical Hemostatic Agents in Obstetric Hemorrhage: International Case Reports

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INTRODUCTION AND BACKGROUND

Topical hemostatic agents are utilized as adjuncts to control intraoperative bleeding when standard surgical techniques (such as suturing, ligature, cautery, or pressure) are insufficient or impractical to implement[1]. Intraoperative scenarios where topical hemostatic agents may serve as adjuncts include bleeding near vital organs or nerves, at needle-holes, from raw surface areas, in friable or attenuated tissue, or in patients who are anticoagulated, have bleeding diatheses, or have platelet dysfunction.

Physical agents and biologically active agents comprise the two main categories of topical hemostatic products. Physical agents promote hemostasis utilizing a passive substrate. Biologically active agents stimulate the coagulation cascade locally at the bleeding site[1].

Biologically active topical hemostatic agents have been marketed in the United States for over 10 years, paralleling the recent advances in biotechnology that resulted in rapid growth of available topical hemostatic agents[2]. Their use for intraoperative hemorrhage control has been described by various surgical specialties, including cardiovascular, otolaryngology, urology, and others[2–6]. Usage in gynecologic surgery has been reported, including laparoscopy, myomectomy, oncologic debulking and inguinal lymphadenectomy[7–11].

In 2007 Moriarty *et al.*[12] (UK) presented a case report on the use topical hemostatic agents in massive postpartum hemorrhage (PPH) in a patient who underwent emergency cesarean delivery due to placental abruption. Approximately 3 hours after cesarean delivery, the patient underwent laparotomy and total abdominal hysterectomy for life-threatening hemorrhage resulting from uterine atony that was unresponsive to conservative measures. The patient developed disseminated intravascular coagulation, and, after hysterectomy, continued to bleed from vascular venous plexuses at the vaginal vault, as well as from suture holes. The topical hemostatic agent comprised of gelatin–thrombin matrix, FloSeal™ (Baxter Healthcare Corporation, Fremont, California, USA), was applied to the bleeding areas. Thereafter, the authors described rapid achievement of hemostasis.

Subsequently, in 2010, Law *et al.* (Hong Kong) reported a case of successful control of persistent PPH from the placental implantation site, using FloSeal[13]. Two hours after cesarean delivery for placenta previa, the patient underwent re-laparotomy for persistent vaginal bleeding, where heavy bleeding from the lower uterine segment was noted. The authors described ineffective suturing for controlling bleeding in the deep placental site, and, therefore, FloSeal was applied. Hemorrhage control was achieved with uterine preservation.

In the same year, Fuglsang and Petersen (Denmark) published a series of 15 cases, delivered by cesarean for placenta previa, where excessive or intractable lower uterine segment hemorrhage was successfully controlled with direct local topical application of hemostatic collagen fleece coated with a mixture of human fibrinogen and thrombin (TachoSil™, Nycomed, Denmark), at the time of cesarean section[14].

Subsequently, in 2011, Tinelli (Italy) reported a case where TachoSil application successfully controlled hemorrhage at the uterine incision site. After a scheduled repeat cesarean section, the patient was found in hemorrhagic shock on postoperative day 3. At re-laparotomy, hemoperitoneum was found, resulting from constant oozing from the uterine incision site and bladder vessels. After ineffective hemostatic suturing, TachoSil was applied with successful hemorrhage control[15].

Similarly, in 2011, Wohlmuth and Dela Merced (US) reported a case of placental implantation site hemorrhage, controlled at the time of cesarean delivery, with gelatin–thrombin matrix (FloSeal) in a patient with placenta previa[16].

In the case reports described, topical hemostatic agents were administered after unsuccessful utilization of traditional PPH treatments. These included uterotonic agents, vessel ligation, uterine compression sutures, packing or balloon tamponade, over-sewing placental bed bleeding sites, recombinant activated factor VII and consideration of uterine artery embolization[17]. The ineffectiveness of the traditional methods of hemorrhage control in the cases of placenta previa was attributed to bleeding from the non-contractile lower uterine segment, large surface areas

of active bleeding, vascular tissue depth at the placental site and tissue friability[13,14,16]. In the event conservative measures fail to control hemorrhage, hysterectomy, generally, is considered as a life-saving procedure.

Where topical hemostatic agents were used successfully at the time of cesarean delivery, re-laparotomy was avoided and uterine preservation was achieved[14,16]. Additionally, with rapid access and successful application of a topical hemostatic agent, the risks of prolonging bleeding time and associated massive blood transfusion can be decreased.

Topical hemostatic agent use in complicated obstetric genital laceration was reported by Whiteside *et al.* (US), in 2010[18]. A 21-year-old primipara patient was found to have a right labial hematoma that developed 2 hours after spontaneous vaginal delivery of twins with immediate repair of vaginal lacerations. The hematoma disrupted the suture line of the original repair. Despite additional suturing and vaginal packing, the hematoma continued to expand, leading to a 10 cm wide hematoma extending from the superior labia majora to the ischial fossa. At surgical exploration and evacuation, poor tissue quality was encountered, with suturing attempts unsuccessful in the presence of friable tissue. Direct pressure applied to the surgical bed did not control hemorrhage, including pressure applied with adjunctive use of microfibrillar collagen hemostat powder, a non-biologically active topical hemostatic agent. With application of biologically active, prohemostatic fibrin sealant (TISSEEL™, Baxter Healthcare Corporation, Fremont, California, USA), hemostasis with tissue sealing was promptly achieved.

In 2009, a similar case of TISSEEL use in managing PPH from obstetric trauma was reported by Dhulkotia *et al.*[19] (UK).

BIOLOGICALLY ACTIVE TOPICAL HEMOSTATIC AGENTS

Because the published case reports of successful topical hemostatic agent use in obstetric hemorrhage are of resorbable biologically active products, the focus of discussion in this chapter is on this category of topical hemostatic agents, specific to those agents reported.

Biologically active topical hemostatic agents stimulate the coagulation cascade, primarily through the transformation of fibrinogen to fibrin by thrombin's enzymatic action (Figure 1).

The multitude of topical hemostatic agents available varies in composition, mechanism of action and method of use. The surgeon should be familiar with the various products' similarities and differences before use[2] (Table 1).

Liquid pro-hemostatic fibrin sealant (TISSEEL) was approved by the United States Food and Drug Administration (FDA) in 1998 as an adjunct to hemostasis in cardiopulmonary bypass and splenic injury surgeries. It is comprised of human fibrinogen and human thrombin. At the time of usage, the two components are combined to produce fibrin, mimicking the final stage of the coagulation cascade[20]. The

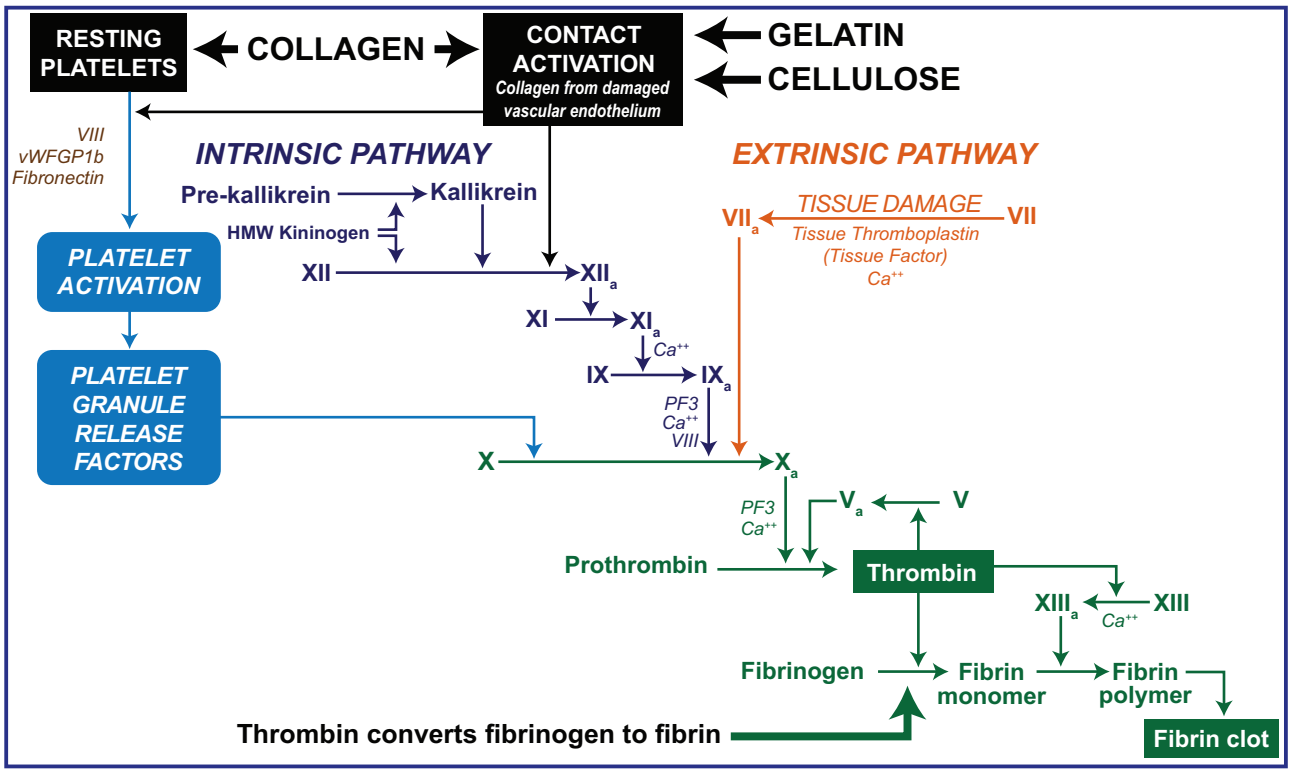

Figure 1 Coagulation cascade. Topical hemostatic agents containing cellulose, collagen, or gelatin stimulate the coagulation cascade through contact activation. Biologically active agents contain, either singly or in combination, thrombin and/or fibrinogen. When combined, thrombin's enzymatic action transforms fibrinogen into fibrin, augmenting the final stages of the coagulation cascade. From Baxter Healthcare Corporation, with permission

Table 1 Topical hemostatic agents in management of postpartum hemorrhage, in published case reports*

Hemostatic agent	*Source*	*Product tradename*	*FDA† approval*	*How supplied*	*Biologically active mechanism*	*Resorption time*	*Recommended use*	*Precautions*
Fibrin sealant spray	Human fibrinogen, human thrombin, synthetic aprotinin	TISSEEL™	1998	Liquid spray	When combined, thrombin's enzymatic action transforms fibrinogen into fibrin, augmenting final stages of coagulation cascade	Immediate	Where tissue adherence is desired in addition to hemostasis	Allergic reaction to aprotinin Do not inject intravascularly Do not use for severe or brisk bleeding. Made from human plasma and may carry risk of transmitting infectious disease
Gelatin–thrombin matrix	Bovine gelatin, human thrombin	FloSeal™	1999	Viscous gel	Upon contact with blood, the fibrinogen source, concentrated thrombin within the gelatin matrix converts fibrinogen into fibrin	6–8 weeks	Range of degrees of bleeding, from oozing to spurting; Where tissue tamponade effect is desired; Irregular wound surfaces	Swell volume 20% Allergic reaction to bovine material Do not inject intravascularly Made from human plasma and may carry risk of transmitting infectious disease Excess FloSeal should be removed by gentle irrigation
Fibrin sealant patch	Equine collagen, human thrombin, human fibrinogen	TachoSil®	2010	Fleece patch	An equine collagen sponge is coated on one side with fibrinogen and thrombin, which, upon contact with physiological fluids, form a fibrin sealant patch	13 weeks††	Large bleeding raw surface areas; Where promoting tissue sealing is desired in addition to hemostasis	Allergic reaction to equine proteins Do not use intravascularly Do not use for severe or brisk bleeding Made from human plasma and may carry risk of transmitting infectious disease Remove unattached pieces

*Off-label use

†Food and Drug Administration, United States.

††TachoSil® Prescribing Information Leaflet, revised: [04/2010]. 12.1 'In animal studies, TachoSil progressively biodegrades with only a few remnants left after 13 weeks. After complete biodegradation, no remnants of the TachoSil patch remained in the body.'

aprotinin component serves as an antifibrinolytic agent. TISSEEL adheres to wound surfaces, achieving hemostasis as well as tissue sealing or gluing. In hemorrhage scenarios, where tissue adherence is desired in addition to hemostasis, liquid fibrin sealant may be preferred.

TISSEEL is supplied as both freeze-dried kits and pre-filled syringes. The freeze-dried kit is stored at 2–25°C. The pre-filled syringe is frozen and stored at –20°C or less. In preparing the freeze-dried kit, to prevent premature clotting, separate syringes are used for reconstituting, as well as applying, the sealer protein and thrombin. In preparing the frozen pre-filled syringe, thawing can be performed at room temperature for up to 48 hours, on the sterile field using 33–37°C sterile water bath, or off the sterile field using water bath or incubator. In geographic regions lacking freezing capabilities, liquid fibrin sealant use is limited to the freeze-dried formulation (Figure 2).

Gelatin–thrombin hemostatic matrix (FloSeal) received FDA approval in 1999 as an adjunct to hemostasis when ligature or conventional procedures are ineffective or impractical. A matrix of bovine gelatin and human thrombin, it provides a concentrated source of thrombin within cross-linked gelatin granules[21] (Figure 3).

To activate the hemostatic matrix coagulation mechanism, blood must be present to provide the fibrinogen source. Upon contact with blood, the concentrated thrombin converts fibrinogen to fibrin. As a high viscosity gel, the gelatin–thrombin matrix fluidity conforms to irregular wound surfaces, thus filling defects and crevices[3,16]. Additionally, gelatin–thrombin matrix provides a tamponade effect, as gelatin granules expand approximately 20% within about 10 minutes of application. Furthermore, FloSeal is described to be 'effective on surgical bleeding, from oozing to spurting'[21]. The combination of fluidity, tamponade and arterial bleed effectiveness deems gelatin–thrombin hemostatic matrix a recommended hemostatic product in cases of irregular wound surfaces or hard-to-reach surfaces and of a range of degrees of bleeding from oozing to spurting[3,21].

Gelatin–thrombin hemostatic matrix is supplied as a freeze-dried kit containing: gelatin matrix in a 10 ml syringe, a vial of human thrombin (lyophilized), a vial of calcium chloride solution, and mixing accessories (bowl for thrombin, two 5 ml syringes, Luer connector and applicator tips). After reconstitution of lyophilized thrombin in calcium chloride solution, gelatin matrix granules are added to the mix by passing thrombin and gelatin between the two syringes. The mixing procedure is reported to take 2 minutes[13] (Figures 4 and 5). FloSeal is stored between 2°C and 25°C (36°F and 77°F), and should not be frozen (see also Chapter 57).

Collagen–thrombin–fibrinogen patch (TachoSil) was granted FDA approval in April 2010 as an adjunct to hemostasis in cardiovascular surgery. An equine collagen sponge is coated on one side with fibrinogen and thrombin[22]. Upon contact with physiological

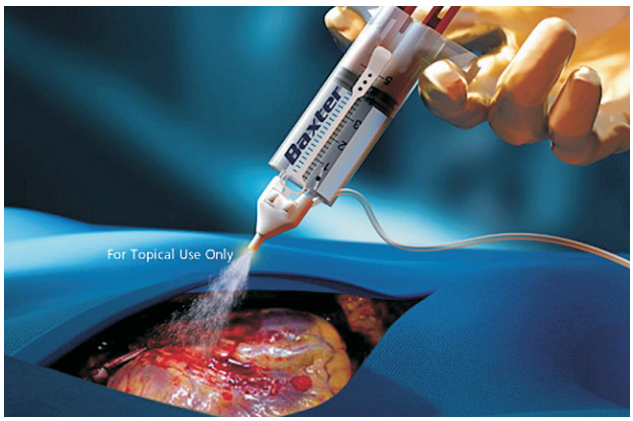

Figure 2 Fibrin sealant liquid spray application. From Baxter Healthcare Corporation, with permission

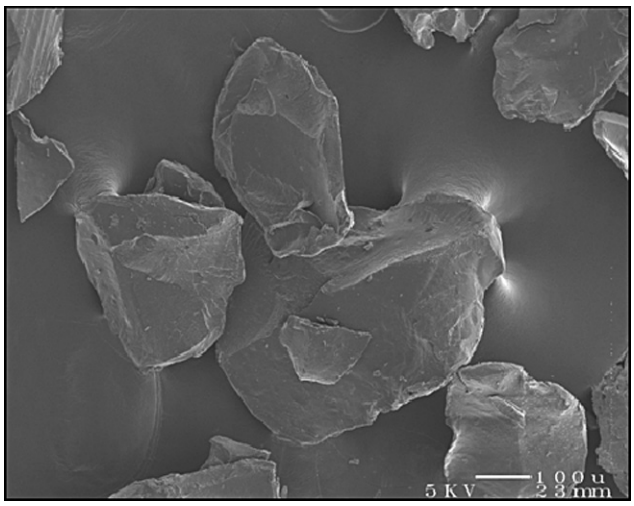

Figure 3 Cross-linked gelatin granules, approximately 0.5 mm diameter, create open spaces that allow high concentrations of thrombin to surround each gelatin particle. From Baxter Healthcare Corporation, with permission

Figure 4 Gelatin–thrombin matrix kit. From Baxter Healthcare Corporation, with permission

fluids or pre-moistening with 0.9% saline solution, the components of the coating dissolve and fibrinogen is converted to fibrin, thus forming a fibrin sealant patch. Supplied in ready-to-use sterile packages, the patch is removed from the blister. The patch can be cut to the appropriate size and shape for the wound, if desired. The patch is applied directly to the bleeding area and pressure applied for at least 3 minutes[22] (Figures 6 and 7). TachoSil should be stored at between 2°C and 25°C (36°F and 77°F). It does not require refrigeration and should not be frozen.

The biologically active topical hemostatic agents discussed contain human plasma, and therefore may carry a risk of transmitting infectious disease despite viral transmission risk reduction procedures applied during manufacturing[20–22]. Hypersensitivity or allergic/anaphylactoid reactions to aprotinin, bovine material and equine material may occur.

Cases of bowel obstruction associated with laparoscopic FloSeal use in gynecologic oncology, urology and general surgery have been reported[23–25]. The presence of excess FloSeal and local inflammatory reaction were suggested as possible etiologies.

As with all medical agents and devices, sound judgment in evaluating risks and benefits of use is required. Topical hemostatic agents are intended to be adjuncts, not substitutes for, meticulous surgical technique and conventional methods to control bleeding. They are not intended for use as prophylactic hemostatic agents[20–22]. Casual use is not advised. In PPH of uterine origin, where conservative or uterine-sparing measures fail to control hemorrhage, hysterectomy is considered a life-saving procedure.

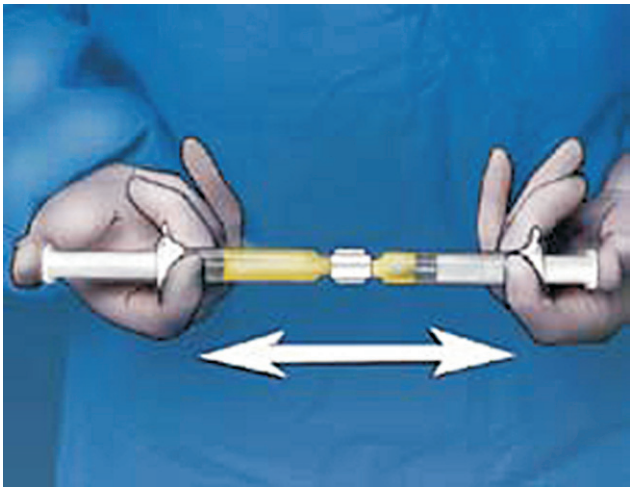

Figure 5 Transfer of gelatin matrix-thrombin solution mixture, back and forth between the syringes. From Baxter Healthcare Corporation, with permission

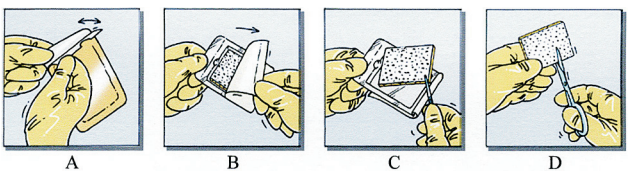

Figure 6 Collagen–thrombin–fibrinogen patch: preparing for application. From Baxter Healthcare Corporation, with permission

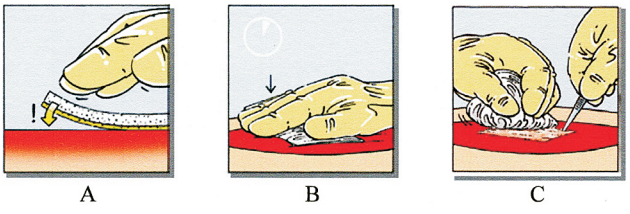

Figure 7 The patch is applied directly to the bleeding area. From Baxter Healthcare Corporation, with permission

AN INSTITUTIONAL EXPERIENCE

White Memorial Medical Center (WMMC) is a nonprofit community hospital located just east of downtown Los Angeles, California, USA. Established in 1913 by the Seventh-day Adventist Church, the hospital's mission is to provide quality health services, medical and health education, and outreach services to the Los Angeles community, with care and compassion. With a capacity of 353 beds, WMMC serves a densely populated, low-income region with more than 2 million residents. Average household income is less than $48,000 a year, with 23% earning less than $25,000 per year. Most of this population is dependent on government-sponsored health care programs. Approximately 85% of the hospital's reimbursement comes from government sources.

The obstetric services at WMMC provide a tertiary referral center, with maternal–fetal medicine consultants and level III neonatal intensive care unit. High-risk obstetric patients are transferred to WMMC from local hospitals for the necessary obstetric and neonatal level of care.

In mid-2011, a retrospective chart review of obstetric services at WMMC, from 2004 to 2010, was conducted to identify cases of postpartum hysterectomy at the time of or within 48 hours of delivery. The review included prenatal records, operative reports, discharge summaries and outpatient postpartum visit notes. During the study period, an average of 3652 deliveries was performed per year. The highest number of deliveries performed during the study period was in the final year of chart review, 2010, with 4148 deliveries. From 2004 to 2010, the cesarean delivery rate increased from 28.5% to 35.5% of all deliveries, similar to the national average[26]. Among all cesarean deliveries, the percentage of repeat cesarean sections gradually increased from 42% to 52% between 2004 and 2010. An average of four postpartum hysterectomies were performed each year, with an incidence of 1 per 1000 deliveries. Abnormal placentation was identified as the most common indication for postpartum hysterectomy.

Our findings are consistent with the study by Rossi *et al.*, who reported abnormal placentation to be replacing uterine atony as the most common indicator leading to emergency postpartum hysterectomy[27].

Our institutional experience includes other obstetric hemorrhage cases that were successfully managed with topical hemostatic agents, in addition to our case report of placenta previa hemorrhage[16].

Case 1

A 35-year-old patient, gravidity 2, parity 1, delivered a term male infant by vacuum assisted vaginal delivery. No vaginal or cervical lacerations were noted. Approximately 3 hours after delivery, the patient reported sudden onset profuse vaginal bleeding associated with Valsalva. At examination, a ruptured vaginal hematoma was noted, extending from the rupture site at the 6 o'clock position in the distal vagina at the level of the introitus, to the full length of the vagina with hematoma dissection of the rectovaginal septum and into the right ischial fossa. The depth of the defect was estimated to be 10 cm. Multiple scattered arterial and venous bleeding sites were diffusely distributed over the length of the rectovaginal septum, which was anatomically distorted by the marked distention of the hematoma. An attempt to suture was ineffective in the presence of friable attenuated tissue and large surface area of bleeding. Because the rectal mucosa was in close proximity and at risk when suturing the surrounding poor quality tissue, use of a topical hemostatic agent was chosen. Gelatin–thrombin matrix was preferred due to the presence of arterial bleeding, large hard-to-reach and irregular surface area, tamponade effect feature and desire for a non-adhering agent in order to leave an open drainage site. Bleeding was controlled in less than 2 minutes after one application of hemostatic gel. In the presence of brisk bleeding, a powder form topical hemostatic agent was not chosen due to risk of being washed away in the flow of blood before adequate polymerization of fibrin could occur.

Case 2

A 44-year-old multiparous patient presented with ruptured amniotic membranes in a pre-viable mid-trimester gestation. After passing the fetus vaginally, the patient developed a prolonged prothrombin time, prolonged activated thromboplastin time and thrombocytopenia, with the total clinical picture consistent with coagulopathy of sepsis. Furthermore, the patient continued to have profuse vaginal bleeding, assessed to be from coagulopathy and possibly placenta accreta, as retained placenta was diagnosed in this patient with prior cesarean deliveries. Coordinating the timing for blood replacement to correct the coagulopathy-based source of bleeding, with the timing for prompt surgical removal of the placental-based source of bleeding, is critical in optimizing outcomes. Continued blood loss, whether from coagulopathy of sepsis or from abnormal placentation or both, can exacerbate the underlying condition with the development of hemorrhagic shock and progressive disseminated intravascular coagulation. As multi-unit blood transfusions were administered, placental delivery was performed by manual removal. Findings were suggestive of placenta accreta. The patient underwent emergency hysterectomy, with intraoperative bleeding consistent with on-going coagulopathy. The pelvic raw surfaces were large, as extensive lysis of adhesions was required in order to complete the hysterectomy. With massive blood transfusion in progress and administration of recombinant activated factor VII[28], control of bleeding at the vaginal cuff and pelvic raw surfaces was achieved with the adjunctive use of gelatin–thrombin hemostatic matrix.

The institutional experience at WMMC is similar to the case reports by Moriarty, Fuglsang and Whiteside[12,14,18].

DISCUSSION

Recent advances in biotechnology have added biologically active features to topical hemostatic agents. These are shown to be effective in controlling intraoperative bleeding in several surgical specialties, including controlled clinical trials of cardiac surgery[3]. In PPH, current literature is comprised of case reports, totaling 20 cases. Seventeen cases were reported for hemorrhage associated with placenta previa[13,14,16]. Two of these were associated with obstetric genital injury[18,19]. One case was associated with disseminated intravascular coagulation at emergency hysterectomy[12].

With a rising cesarean delivery rate[26] and the associated increased risk for placenta previa and placenta accreta[29], the presence of 17 cases in the literature of PPH associated with placenta previa successfully managed with resorbable bioactive topical hemostatic agent invites further investigation and consideration for both adjunct and primary treatment with topical hemostatic agents[13,14,16].

As an adjunct intervention when standard surgical methods fail to control hemorrhage, topical hemostatic agents may have a more primary role where surgical intervention is difficult, such as in under-resourced geographic regions, with limited or no access to emergency surgical facilities, blood banking resources, parenteral administration of medication capabilities and invasive radiology embolization. Availability and accessibility of topical hemostatic agents, with features of quick preparation and easy application, may decrease morbidity and mortality associated with delayed treatment of hemorrhage.

Although the use of topical hemostatic agents in managing PPH in peer-reviewed literature is limited to case reports, further studies may provide information to solidify topical hemostatic agents as an adjunct or primary treatment in PPH.

The authors have no financial interest or other relationship with the manufacturers of the products discussed in this manuscript.

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