Case Series

The Efficacy of BloodSTOP iX, Surgicel, and Gelfoam in Vascular Operations: First-in-Human Head-to-Head Study

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Abstract

This study aims to compare the efficacy and safety of 3 different hemostatic agents in vascular surgeries in humans. Twenty-four patients were enrolled in the present study with 40 vascular anastomoses including 16 aortic and 24 femoral. The patients were randomized (computer-based) to either BloodSTOP iX, Gelfoam, or Surgicel. The hemostatic agent was applied at the site of the vascular anastomosis before declamping. The site of anastomosis was then observed for bleeding from the suture line for 2 min. If any bleeding was detected, blood was then collected for 5 min, and the time needed to stop bleeding was measured. A suction drain was fixed in the surgical bed to collect serous fluid postoperatively more than 48 h afterward. The volume of blood collected in 5 min was significantly lower in the BloodSTOP group compared with the other 2 hemostatics. There was a significant reduction in the mean time needed to stop bleeding from the anastomotic surface in the BloodSTOP group compared with the Surgicel and Gelfoam groups. In addition, Surgicel showed the highest rate of complication (46.2%) compared with BloodSTOP (7%). BloodSTOP iX dramatically reduced bleeding volume and time compared with the other hemostatic agents. Furthermore, it showed a lower complication rate and did not interfere with the healing process at the application sites.

Keywords

BloodSTOP iX, Surgicel, Gelfoam, hemostasis in humans

Introduction

The control of hemorrhage is a critical step in vascular surgery. Unfortunately, the methods available to stop bleeding in prehospital care (e.g., gauze dressings, direct pressure, and tourniquets) have not changed greatly in 2,000 years.[1] Animal studies comparing the efficacy of 3 different hemostatic agents found BloodSTOP iX (LifeScience Plus, Mountain View, CA, USA) to be superior. Compared with Surgicel (Ethicon, Raritan, NJ, USA) and Gelfoam (Pfizer, New York, NY, USA), BloodSTOP iX had the lowest mean average bleeding time of any of the 3 products.[2] BloodSTOP iX is a developed, potent hemostatic material made of water-soluble cellulose ether derivatives (carboxymethyl sodium). There are a wide array of uses for BloodSTOP iX including internal or external applications, namely, neurosurgery, stomatology, nasal, abdominal surgery, chest surgery, hemorrhoids, and prevention of operative adhesion.[3] Featuring a dual mode of action, once BloodSTOP iX is exposed to blood or any other body fluids, it turns into a gel and physically seals the bleeding site within 6 to 12 s. In addition, it acts biologically by initiating and promoting platelet activation and aggregation as well as activation of intrinsic coagulation cascade.[3] BloodSTOP iX can substantially shorten thromboplastin time and is superior to water-insoluble oxidized cellulose and gelatin sponge.[3] Animal studies showed the advantages of BloodSTOP iX as an oxidized cellulose-based product, and it can therefore accelerate thrombin generation in the body,[4] which is necessary for the intrinsic coagulation pathway. The polysaccharide meshwork of the product also works as a framework to support coagulation.[5,6] A major benefit of the BloodSTOP iX product is the ease of removal without the disruption of the clot that has formed underneath. Although the advantages of BloodSTOP iX over other hemostats have been proven in animal models, no studies were conducted in humans. The current study aimed to compare the efficacy and the ability to control bleeding among different hemostatic agents in human vascular surgeries.

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Case Series

This randomized prospective study was conducted in the Department of Vascular Surgery from 2020 to 2021. Randomization was double anonymized and computer based. Simple random sampling was done using computer-generated random tables by the IBM SPSS Statistics program (IBM Corp, Armonk, NY, USA) using a sampling frame of all cases eligible for the surgical technique. The principal investigator ran the program nonanonymized for the hemostatic selection. Anonymization was not possible intraoperatively. However, the material selection was predetermined before the start of the surgery. Assessors as well as statisticians were anonymized to the materials used intraoperatively, as these data were available only to the principal investigator. A CONSORT flow chart of anastomoses assigned to the hemostats depicts the study design (Supplemental Material).

The primary outcome included primary hemorrhage (reflected by the mean time to stop bleeding) and residual particles around the anastomosis (represented by the remaining hemostat after biodegradation). Secondary outcomes included pseudoaneurysm, infection, secondary hemorrhage, and wound dehiscence.

All types of vascular surgeries were included in which vascular anastomosis is utilized with a minimum of 10 mm stoma in large and medium-sized arteries. Exclusion criteria included platelets less than 100,000, infected vascular bed, and patients who refused to sign the consent.

Data Collection

The demographics, symptoms, preoperative clinical data, underlying medical conditions, and associated morbidity were collected. Detailed vascular examinations and workups including blood picture, blood sugar level, kidney functions, liver functions, and coagulation profile were done preoperatively. The coagulation profile was normal in all patients; 5,000 units of heparin were administered before clamping and were not reversed by protamine. Informed consent of possible complications pertinent to the procedure and available alternatives were obtained. Twenty-four patients were enrolled in the present study with 40 vascular anastomoses, including 16 aortic and 24 femoral. All anastomoses were done by or under the supervision and assistance of the principal investigator. The patients were randomized (computer based) to either BloodSTOP iX, Gelfoam, or Surgicel. Dacron was the conduit used for the bypass. The mean age of the patients was 45 years, with 20 males and 4 females. Ten patients had combined comorbidity of diabetes mellitus, hypertension, and smoking, while the rest consisted of 4 smokers, 3 patients with diabetes, and 2 patients with hypertension (Table 1). After completion of the vascular anastomosis and securing the suture line, the hemostatic agent was then applied in 2 layers in the case of BloodSTOP (Fig. 1a) and 4 layers for the other 2 hemostatics, as recommended by the instructions for use. Extreme precaution was taken not to touch any fluid before the hemostatic was applied to the suture line. Vascular anastomosis was observed for the presence of bleeding from the suture line (if any), blood was then collected for 5 min (Fig. 1b), and the time needed to stop bleeding was measured. It is noteworthy that none of the cases needed reclamping to control bleeding at the suture line following the initial declamping. Suction drainage was fixed in the surgical bed to collect serous fluid postoperatively for more than 48 h in the aortic anastomosis and through the PICO system (Smith & Nephew, London, UK) for the femoral

Table 1. Demographic Data of Enrolled Patients.

Demographics	Value
Age, years	57.20 ± 4.81 (45–63)
Sex	
Male	20
Female	4
Medical history	
Smokers only	4
Diabetes mellitus only	3
Hypertension only	2
Hypertension, diabetes, and smoker	10
Platelets	186.40 ± 10.98 (160–206)
INR	1.15 ± 0.16 (1.0–1.4)
Operation	
Aortic anastomosis	16
Femoral anastomosis	24

Abbreviation: INR, international normalized ratio.
Data are reported as mean ± SD (min–max) or *n*.

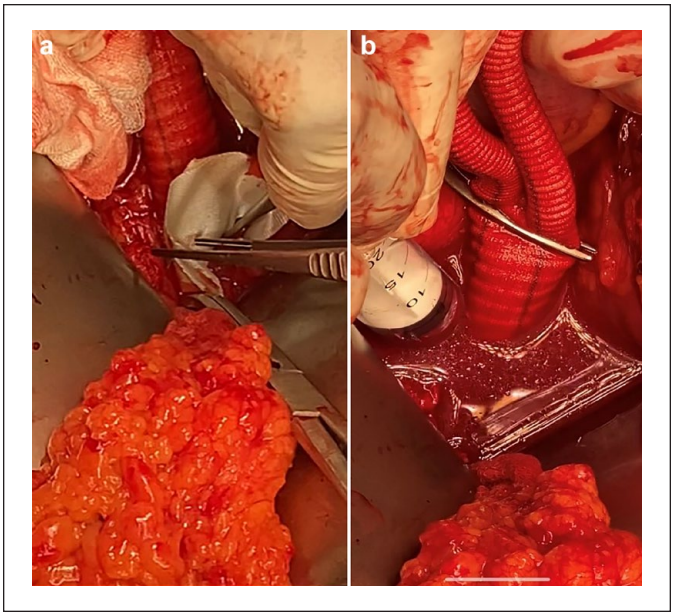

Fig. 1. (a) BloodSTOP iX (LifeScience Plus, Mountain View, CA, USA) was applied around the suture line of aortic anastomosis in 2 layers. (b) Collection of blood accumulating around the suture line for 5 min.

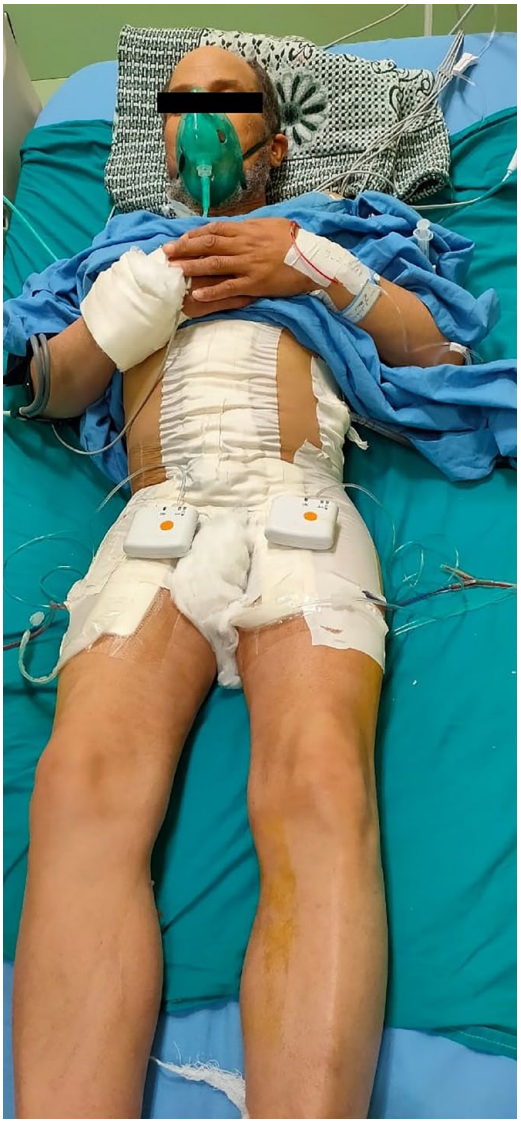

Fig. 2. PICO system (Smith & Nephew, London, UK) was applied for the femoral wounds to collect any fluid discharge.

incision (Fig. 2) and closed suction for the aortic bed. The wounds were monitored for signs of infection, dehiscence, or secondary hemorrhage. Doppler ultrasound examination was then performed 2 days, 2 weeks, and 1 month postoperatively to check for residual material of the hemostat and the development of pseudoaneurysms at the anastomotic line. Informed consent was obtained from all patients for publication as well as approval by the institutional review board committee of the Faculty of Medicine (reference number: R.21.01.1142. R1.R2-2021/02/10).

Statistical Analysis

The data were analyzed using IBM SPSS Statistics. The numerical outcomes (e.g., age) were calculated as means. Gender was recorded as frequency and percentage. The chi-square test was applied to assess the association of various parameters. The results were considered statistically significant if a P value <0.05 was found.

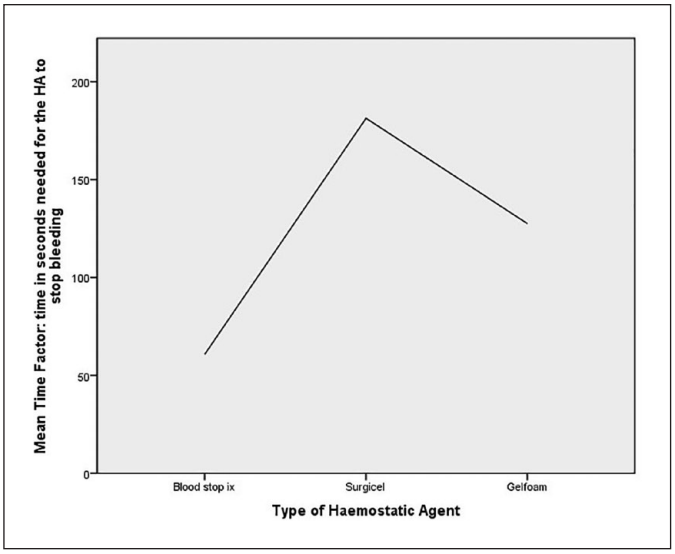

Fig. 3. Time in seconds needed to stop bleeding at the suture line.

Results

BloodSTOP iX was applied to 12 aortic and 2 femoral anastomoses while Surgicel was applied to 2 aortic and 11 femoral anastomoses. Gelfoam was applied to 2 aortic and 11 femoral anastomoses as well. There was no bleeding at the application site for 2 min in 10 anastomoses of BloodSTOP iX (71.4%), 7 anastomoses of Surgicel (53.8%), and 8 anastomoses of Gelfoam (61.5%). On the occasion of bleeding, the mean time needed to stop the bleeding was 61 s for BloodSTOP iX, 181 s for Surgicel, and 127 s for Gelfoam (Fig. 3). The volume of blood accumulated in 5 min of application was 39 mL, 189 mL, and 139 mL for BloodSTOP iX, Surgicel, and Gelfoam, respectively (Fig. 4).

The volume of blood or serosanguineous fluid collected in the drain within 48 h postoperatively was 39 mL (average 27 to 66 mL) in 12 patients (86%) with BloodSTOP iX compared with 170 mL (average 150 to 200 mL) in 11 patients (84%) with Surgicel and 190 mL (average 165 to 230 mL) in 10 patients (77%) with Gelfoam, with a statistically significant difference in favor of BloodSTOP iX ($P < 0.001$).

Ultrasonography performed 2 days postoperatively showed residual particles in 86% of cases of BloodSTOP iX compared with 100% of cases of Surgicel and 92% of cases of Gelfoam. Later, after 2 weeks postoperatively, there were no residual particles in the BloodSTOP group, but there were remnants in 86% and 69% of the Surgicel and Gelfoam groups, respectively (Table 2).

Follow-up for complications revealed only 1 case of turbid fluid and culture-evidenced infection in the BloodSTOP iX

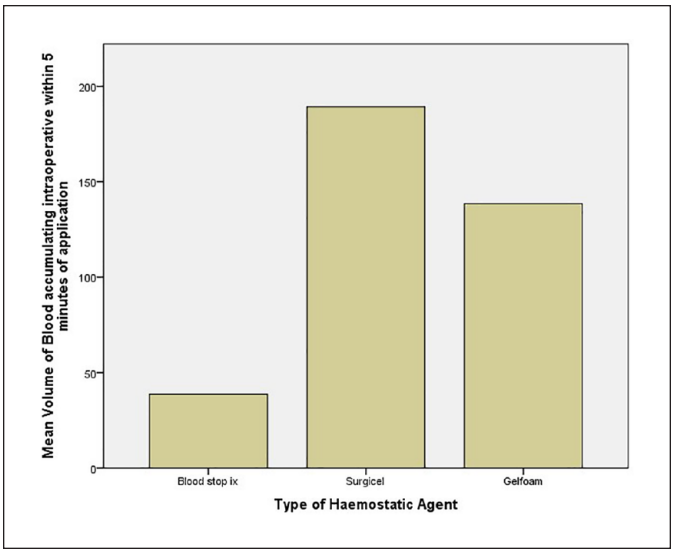

Fig. 4. Mean volume of blood collected in 5 min at the suture line.

group at the femoral anastomosis. However, no other complications were detected in the rest of the patients. On the other hand, the Surgicel group displayed complications in 46.2% of the cases including 2 cases of infection, 1 case of secondary hemorrhage, and 3 cases of wound dehiscence. In addition, the Gelfoam group showed complications in 15.4% of the cases including 1 case of infection and 1 case of wound dehiscence. All forms of infection were found to be of wound origin without graft containment except for 1 in the Surgicel group, which progressed to secondary hemorrhage due to disruption of the femoral anastomosis 11 days postoperatively.

Discussion

Direct pressure is the most effective preliminary hemostasis method. However, topical hemostatic materials are used to assist in the sealing of vascular anastomosis.[4] Hemostatic dressings are substantially feasible for compressible vascular injuries inappropriate for tourniquets, such as those in the neck, axilla, or groin.[7] A wide variety of dressings have been tested for this purpose,[8] including Kaolin-impregnated gauze, which is the only hemostatic agent with no mortality in a swine model of groin injury.[9] Fibrin sealants are hemostatic agents derived from human plasma that mimic the final steps in the coagulation pathway forming a stable fibrin clot. Fibrin sealants are used in a wide range of surgical procedures to assist hemostasis.[10]

BloodSTOP iX is a woven fiber matrix made from regenerated cotton cellulose. When hydrolyzed by water, it becomes a gel that can adhere to the bleeding surface and vascular anastomosis.[11] These aforementioned characteristics allow swift sealing of the bleeding surface at the vascular anastomosis and faster achievement of hemostasis. BloodSTOP is biocompatible, nonirritating, and water soluble; quickly absorbs blood; and transforms into a gel with a protective transparent layer. The translucency of the gel also allows for monitoring of the healing process without removing the matrix. It is 100% natural cellulose and easily removed without disruption of the wound surfaces after hemostasis.

In the present study, the hemostatic agents were applied to large and medium-sized vessels exclusively on the aorta and femoral arteries with the highest peak velocity, including 120 to 150 cm/s for the aorta and 80 to 110 cm/s for the femoral artery.[12] Moreover, the efficacy of hemostatics was tested against the highest pressure after declamping of the aorta while still clamping the graft distal to the anastomosis as the mean arterial pressure increased by more than 50%.[13]

The average resting common femoral artery flow rate that is clinically unaffected by peripheral vascular disease is 350 $\pm$ 141 mL/min, which is higher than other peripheral arteries.[14] The observation that 71% of the BloodSTOP group, 61% of Gelfoam group, and 53% of the Surgicel group did not show bleeding at the vascular anastomosis in the first 2 min but without a statistically significant difference is substantially related to the mechanical effect on the bleeding surface, which is indifferent between the applied agents. On the other hand, the volume of blood collected in 5 min was significantly lower in the BloodSTOP group compared with the other 2 hemostatics, which reflects its effect on platelet activation and initiation of a platform of coagulation cascade ending up with sealing of the bleeding surface. Moreover, there was a significant reduction in the mean time needed to stop bleeding from the anastomotic surface in the BloodSTOP group compared with the Surgicel and Gelfoam groups. This observation had been reported in experimental studies demonstrating the efficacy and safety of BloodSTOP iX using a widely recognized 6 mm femoral artery injury model in swine.[2,15] Bleeding time was compared in another study with a rat model of partial nephrectomy and aortic needle injury using 3 different hemostatic agents.[16] BloodSTOP iX was more effective in reducing the bleeding time than Surgicel in a rat model of partial nephrectomy. Correspondingly, in an aortic needle injury model, BloodSTOP iX achieved hemostasis faster than Gelfoam or Surgicel did.[16] The volume of fluid collected postoperatively was much less in the BloodSTOP group than in the other 2 groups, which reflects the natural, neutral, nonirritant, biocompatible characteristics of BloodSTOP with minimal inflammatory reaction to the surrounding tissues. This is in contrast to Surgicel, which is formed of polyanhydroglucuronic acid with a pH of 3 that may induce intense inflammatory exudate and reduce the healing process.[17]

Herein, we report the total absorption of BloodSTOP from the surgical site within 2 weeks compared with a significant percentage of residual material in Surgicel (86%) and Gelfoam (69%). The esterification of oxidized regenerated cellulose (ORC) in the BloodSTOP iX resulted in multiple advantages, including water solubility and biodegradability, leaving no residue behind, in addition to the lack of fluid encapsulation and foreign body reaction. On the contrary, Gelfoam, which is

Table 2. Comparative Analysis of Hemostat Data.

	BloodSTOP iX	Surgicel	Gelfoam	*P* value
Operation				<0.001
Aortic anastomosis	12	2	2	
Femoral anastomosis	2	11	11	
Observation of bleeding at application site for 2 min				0.639
No	10	7	8	
Yes	4	6	5	
Time needed for hemostatic agent to stop bleeding, sec [a]	61	181	128	<0.001
Volume of blood accumulated intraoperatively within 5 min of application [a]	39	189	139	<0.001
Volume of blood or fluid in drain on second day				0.094
<50 mL	12	6	8	
>50 mL	2	7	5	
Residual particles around the anastomosis via ultrasonography				
Before discharge	12	13	12	0.06
2 weeks	0	11	9	0.001
Follow-up at 2 to 4 weeks				0.091
No complications	13	8	11	
Pseudoaneurysm	0	0	0	
Infection	1	2	1	
Secondary hemorrhage	0	0	0	
Wound dehiscence	0	3	0	
Follow-up at 6 to 8 weeks				0.170
No complications	14	12	12	
Pseudoaneurysm	0	0	0	
Infection	0	0	0	
Secondary hemorrhage	0	1	0	
Wound dehiscence	0	0	1	
Follow-up at 6 months				0.378
No complications	14	13	13	
Pseudoaneurysm	0	0	0	
Infection	0	0	0	
Secondary hemorrhage	0	0	0	
Wound dehiscence	0	0	0	
Complications				0.040
No	13	7	11	
Yes	1	6	2	

[a]Data are reported as mean.

made from acid partial hydrolysis of porcine-derived collagen, is absorbed after 6 weeks. Gelatin absorbs blood up to 40 times its weight and expands to 200% of its original dimensions, resulting in some safety issues such as overswelling when used within small spaces. For this reason, it is not used intravascularly.[18] ORC products remain for a longer time, being absorbed within 8 weeks. ORC products should not be used in closed spaces as well due to potential swelling or for control of bleeding from large arteries.[18]

Multiple complications have been reported with the use of Surgicel in abdominal and neurosurgical procedures, including granuloma, pseudo abscess, paraplegia, prolonged drainage, and obstructive uropathy.[19–21] Surgicel is associated with yellowish thick discharge either in the form of prolonged drainage or pseudo abscess-like presentation. This report is in line with our observation that Surgicel showed the highest rate of complication (46.2%) compared with BloodSTOP (7%). Surgicel must be used in the smallest possible amount because of its foreign nature.[20] The drainage is applied for only 48 h to collect the fluid (blood or serosanguinous) representing the efficacy of the hemostat in controlling bleeding from the suture line to prevent primary bleeding and inflammatory response of the tissues to the hemostat. Beyond the 48 h, any fluid collection represents lymphorrhoea or pyogenic material, which is unrelated to the hemostat but is related to the operation itself including the preoperative aseptic precautions and the operative meticulous dissection and sparing the inguinal lymph nodes to avoid the lymphorrhoea. In this setting, the limitation of fluid collection to 48 h results in indifference between the femoral and aortic location, while the single independent factor determining the

amount of fluid will be the hemostat, either through insufficient bleeding control or the exaggerated tissue response.

In vascular practice, the achievement of rapid hemostasis provides a plethora of benefits including better visualization of the surgical field, shorter operative times, minimal transfusion requirement, better bleeding control of anticoagulated patients or those with bleeding tendency, shorter wound-healing time, and overall improvement in patient recovery time. A staggering demand for a safe and efficacious hemostatic has been rising for years. In the present study, BloodSTOP iX seems to achieve this goal by covering most of the demands for the appropriate hemostat, namely, the biodegradability, minimal irritation by the virtue of its neutral pH, trivial inflammatory reaction and wound discharge, significant reduction of the bleeding time, and formation of transparent gel layer for better visualization of the suture line, as well as no interference with wound healing.

Limitations of the Study

Small sample size, a discrepancy in anastomotic artery thickness, and the presence of residual plaque after endarterectomy were limitations. In aortic anastomoses, needle sizes were different from those used in the femoral artery. In addition, wall tension was different between large and medium-sized vessels.

Conclusions

BloodSTOP iX is safe and effective for achieving vascular anastomosis hemostasis. BloodSTOP iX dramatically reduced bleeding volume and time compared with the other hemostatic agents. BloodSTOP iX showed a lower complication rate and did not interfere with the healing process at the application sites.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

References

1. Zimmerman L and Veith I. *Great ideas in the history of surgery*. San Francisco: Norman Publishing, 1993.
2. Sileshi B, Achneck HE and Lawson JH. Management of surgical hemostasis: topical agents. *Vascular* 2008; 16: S22–S28.
3. Aubourg R, Putzolu J, Bouche S, et al. Surgical hemostatic agents: assessment of drugs and medical devices. *J Vasc Surg* 2011; 148: e405–e408.
4. Rysava J, Dyr JE, Homola J, et al. Surface interactions of oxidized cellulose with fibrin(ogen) and blood platelets. *Sens Actuators B Chem* 2003; 90: 243–249.
5. Larson PO. Topical hemostatic agents for dermatologic surgery. *J Dermatol Surg Oncol* 1988; 14: 623–632.
6. Morrison JJ, Mountain AJ, Galbraith KA, et al. Penetrating pelvic battlefield trauma: internal use of chitosan-based hemostatic dressings. *Injury* 2010; 41: 239–241.
7. Wright FL, Hua HT, Velmahos G, et al. Intracorporeal use of the hemostatic agent QuickClot in a coagulopathic patient with combined thoracoabdominal penetrating trauma. *J Trauma* 2004; 56: 205–208.
8. Littlejohn L, Bennett BL and Drew B. Application of current hemorrhage control techniques for backcountry care: part two, hemostatic dressings and other adjuncts. *Wilderness Environ Med* 2015; 26: 246–254.
9. Bennett BL, Littlejohn LF, Kheirabadi BS, et al. Management of external hemorrhage in tactical combat casualty care: chitosan-based hemostatic gauze dressings–TCCC guidelines-change 13-05. *J Spec Oper Med* 2014; 14: 40–57.
10. Acheson EM, Kheirabadi BS, Deguzman R, et al. Comparison of hemorrhage control agents applied to lethal extremity arterial hemorrhages in swine. *J Trauma* 2005; 59: 865–874.
11. Mankad PS and Codispoti M. The role of fibrin sealants in hemostasis. *Am J Surg* 2001; 182(2 Suppl): 21S–28S.
12. Dowling MB, Kumar R, Keibler MA, et al. A self-assembling hydrophobically modified chitosan capable of reversible hemostatic action. *Biomaterials* 2011; 32: 3351–3357.
13. Brant WE. *The core curriculum: ultrasound*. Philadelphia: Lippincott, Williams & Wilkins, 2001.
14. Roizen MF, Beaupre PN, Alpert RA, et al. Monitoring with two-dimensional transesophageal echocardiography: comparison of myocardial function in patients undergoing supra-celiac, suprarenal-infraceliac, or infrarenal aortic occlusion. *J Vasc Surg* 1984; 1: 300–305.
15. Liang HL. Doppler flow measurement of lower extremity arteries adjusted by pulsatility. *Am J Roentgenol* 2020; 214: 10–17.
16. Ferretti L, Qiu X, Villalta J, et al. Efficacy of BloodSTOP iX, Surgicel, and Gelfoam in rat models of active bleeding from partial nephrectomy and aortic needle injury. *Urology* 2012; 80: 1161–1166.
17. Ibarrola JL, Bjorenson JE, Austin BP, et al. Osseous reactions to three hemostatic agents. *J Endod* 1985; 11: 75–83.
18. Vyas KS and Saha SP. Comparison of hemostatic agents used in vascular surgery. *Expert Opin Biol Ther* 2013; 13: 1663–1672.
19. Mohamed FI, Christopher AP and Christopher PY. A foreign body reaction to Surgicel mimicking an abscess following cardiac surgery. *Eur J Cardiothorac Surg* 2002; 22: 489–490.
20. Patanè F, Zingarelli E, Verzini A, et al. Complication due to excessive use of Surgicel. *Eur J Cardiothorac Surg* 2001; 20: 1075–1076.
21. Sandhu GS, Elexpuru-Camiruaga JA and Buckley S. Oxidized cellulose (Surgicel) granulomata mimicking tumor recurrence. *Br J Neurosurg* 1996; 10: 617–619.