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Efficacy of topical hemostatic agents in neurosurgery: An experimental study in a rat model

Florencia Casto[1], Miguel Villaescusa[1], Ezequiel Jungberg[1], Tomas Saavedra Azcona[1], Delfina Lanusse[2], Pedro Plou[1], Matteo Baccanelli[1], Pablo Ajler[1]

Departments of [1]Neurosurgery and [2]Anesthesiology, Hospital Italiano de Buenos Aires, Ciudad Autonoma de Buenos Aires, Argentina.

E-mail: *Florencia Casto - florencia.casto@hospitalitaliano.org.ar; Miguel Villaescusa - miguel.villaescusa@hospitalitaliano.org.ar; Ezequiel Jungberg - ezequiel.jungberg@hospitalitaliano.org.ar; Tomas Saavedra Azcona - tomas.saavedra@hospitalitaliano.org.ar; Delfina Lanusse - delfina.lanusse@hospitalitaliano.org.ar; Pedro Plou - pedro.plou@hospitalitaliano.org.ar; Matteo Baccanelli - matteo.baccanelli@hospitalitaliano.org.ar; Pablo Ajler - pablo.ajler@hospitalitaliano.org.ar

***Corresponding author:**
Florencia Casto,
Department of Neurosurgery, Hospital Italiano de Buenos Aires, Ciudad Autonoma de Buenos Aires, Argentina.

florencia.casto@hospitalitaliano.org.ar

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ABSTRACT

Background: Few studies have compared different topical hemostatic agents in live models or brain tissue, and their doses are not standardized. Little is known about the combined use of these different elements in terms of efficacy and safety, especially in neurosurgery. The objective of this study was to evaluate the efficacy of different topic hemostatic agents used in daily neurosurgical practice in an experimental animal model study.

Methods: A group of 42 Wistar rats was used. A stereotaxic frame was fixed, and coordinates were determined to locate the bregma. A 3 mm hole was drilled with a bone-profile burr on each side of the midline. A stylet was inserted into the brain to create the defect and induce bleeding. The rats were randomly divided into seven groups, with each group assigned a hemostatic agent. Hemostasis time and control time on the opposite side were measured.

Results: Hemostasis was achieved after an average of 1 82 s in the group treated with Beriplast, making it the hemostatic agent that stopped the bleeding the fastest. The control time was an average of 40, 14 s. Compared with the negative control, all the agents resulted in significantly better hemostasis ($P < 0.05$).

Conclusion: A reduction in postoperative bleeding positively impacts annual morbidity and mortality rates, hospitalization time, and hospital bed turnover. Understanding the efficacy and safety of different hemostatic agents will enable surgeons to optimize intraoperative hemostasis, thereby achieving better postoperative outcomes and increased patient safety.

Keywords: Coagulation, Experimental study, Hemostasis time, Rat model, Topical hemostatic

INTRODUCTION

Hemostasis can be described as a tightly regulated process that ensures that blood flow is maintained through the vascular system while a thrombotic response to tissue injury takes place. Controlling hemostasis is a critical stage in any surgical intervention and involves complex interactions among the vascular wall, platelets, and the balance between coagulation and fibrinolysis.[7] Continuous and uncontrolled bleeding from smaller capillaries or small veins during surgery can invade the surgical field, reduce visibility, prolong surgical time, increase the risk of postoperative complications, and even require blood transfusions.[13,14] While bleeding up

to a liter can be tolerated in structures such as the abdominal cavity, bleeding of just a few milliliters intracranially or the spinal canal can cause devastating neurological damage.[13,14] In neurosurgery, bipolar coagulation, careful manual compression, and a variety of topical hemostatic agents are typically used as adjuncts to minimize bleeding. Mechanical hemostasis methods such as direct pressure and ligation are not preferred in neurosurgery due to the depth and characteristics of neurovascular structures.[13,14] With respect to bipolar cauterization, complete occlusion of a vessel's lumen can compromise the perfusion of tissue supplied by the coagulated vessel.[14,17] Chemical hemostatic agents are typically preferred because they control bleeding without occluding the vessel lumen and do not cause thermal damage to surrounding tissues.[14] However, they can have variable efficacy and prolonged degradation and elimination times.[3] Residual hemostatic material can serve as a nidus for infection and even induce a foreign body reaction with granuloma formation on histological examination.[1,6] Topical hemostatic agents are classified into active and passive. Passive agents, which are not biologically active[5], consist of collagen, cellulose, and gelatin and work by contact to activate and enhance platelet aggregation. Active hemostatic agents, such as fibrin and sealants, including thrombin, act biologically on the patient's coagulation mechanism.[1] Few studies have compared different hemostatic agents in live models or brain tissue, and there is no standardization regarding their doses.[7] Little is known about the combined use of these products in terms of efficacy and adverse effects, especially in neurosurgery. This study analyzed agents derived from regenerated oxidized cellulose (Surgicel, absorbable hemostatic, Ethicon Inc., New Brunswick, New Jersey), fluid porcine gelatin combined with human thrombin (Surgiflo, hemostatic matrix, Ethicon Inc., New Brunswick, New Jersey), and fibrinogen combined with human thrombin (Beriplast, CSL Behring, Germany), which were used alone and in combination with platelet-rich plasma (PRP). We aimed to standardize the amount of hemostatic product needed to achieve bleeding cessation in cerebral parenchyma lesions in rats, measured in mL or cm^3 according to the product, and to determine whether combining the commercial hemostatic product with PRP enhances its efficacy, either by reducing the hemostasis time, the amount of product required for this purpose, or both. We intended to record any complications and/or adverse effects associated with the topical administration of these hemostatics in rat brain tissue, whether used alone or in combination.

MATERIALS AND METHODS

Surgical protocol and planning

This study used a group of 42 adult Wistar rats (weighing between 400 and 600 g, aged 3–4 months). This protocol was evaluated and approved by the Institutional Committee for the Care and Use of Laboratory Animals of our hospital, and animal handling was performed in accordance with their policies and the Guide for the Care and Use of Laboratory Animals. Informed consent was not needed. This study was conducted on rat brains because their circulation and brain anatomy are similar to those of humans.[8] The Rat Brain Atlas Collection in Stereotaxic Coordinates (Khazipov *et al*., 2015) was used as a reference.[9] A target for the craniotomy was chosen 3 mm from the bregma on the coronal plane bilaterally. The bregma has been widely described and used as a reference point for stereotaxic coordinates in rodents, but its measurement is highly heterogeneous among laboratories.[4] Therefore, specific coordinates were determined for each animal on the basis of age and sex to perform the lesion in a cortical area without vascular involvement, thereby standardizing the procedure and reducing variations and potential complications. Since this was a dynamic study evaluating the coagulation cascade and cerebral circulation, the use of an artificial or *in vitro* model was excluded. Before the experiment, a 12:12 h light/dark cycle was established, access to food and water was provided ad libitum, and the temperature was maintained within a stable range.

Experimental phase

The animal was weighed, and general anesthesia was administered with a dose of 10 mg/kg xylazine and 80 mg/kg ketamine intramuscularly under the care of a specialized veterinarian. After induction, the reflexes were checked to ensure complete anesthesia. The rats were randomly distributed into seven groups, each assigned a topical hemostatic agent. The hemostatic agent, if necessary, was prepared immediately before the procedure by the surgeon [Figure 1]. The same operator performed all procedures to reduce variability between surgeons. The skin was shaved, and a stereotaxic frame (Stoelting, Illinois, USA) with predefined coordinates was used to perform the trephine hole bilaterally at the same site in all the rats. A surgical microscope was used. A sagittal incision was made in the skin, which was retracted to expose the skull. A 3 mm hole was made at the predefined coordinates with a bone drill [Figure 2]. A small cross-shaped durotomy was performed, and a metallic needle was inserted 2 mm into the brain to create the defect and induce bleeding. The animals were randomly assigned to one of the seven groups; each assigned a topical hemostatic agent or a combination of two of them. These were chosen among the approved topical hemostatics for neurosurgery [Table 1]:

1. Regenerated oxidized cellulose (Surgicel, Absorbable Hemostatic, Ethicon Inc., New Brunswick, New Jersey): available in sizes of 3 × 2 in, 8 × 4 in, 14 × 2 in, or 2 × 1.5 in, mesh forms that can be cut as needed. A key advantage is that it is immediately ready for use, unlike

Table 1: Classification of hemostatic and topical sealant agents on the basis of Emilia *et al.*[5]

Category	Product	Origin	Active ingredients	Mechanism of action
Adhesive hemostatics	EVICEL	Human	Human fibrinogen+human thrombin	Thrombin and fibrinogen combine at the time of application. Thrombin breaks down fibrinogen into fibrin, forming a clot.
	Tissucol	Human//animal	Human fibrinogen+human thrombin	
	Beriplast	Human//animal	Human fibrinogen+human thrombin	
	TachoSil	Human//animal	Equine collagen+fibrinogen and thrombin	
Topical hemostatics	Surgicel	Vegetal	Regenerated oxidized cellulose	It is a physical matrix for clot initiation. The low pH promotes the antimicrobial effect.
	Surgiflo	Animal/human	Porcine gelatin+Human thrombin	Provides a matrix for platelet adhesion, accelerating the formation of the platelet plug and fibrin clot
	FloSeal	Animal	Bovine collagen+Bovine thrombin	
	Spongostan	Animal	Porcine gelatin	As blood is absorbed by the sponge, platelets and clotting factors are activated, leading to the formation of a stable fibrin clot.

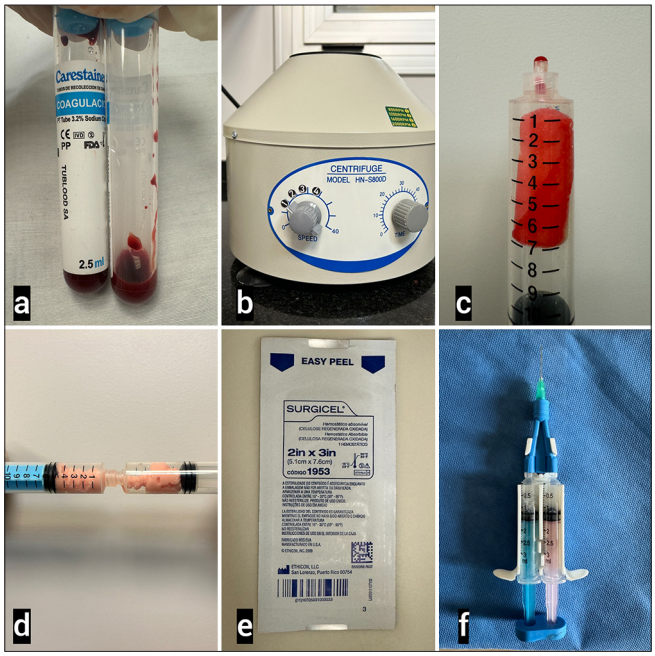

Figure 1: Preparation of Hemostatic Agents. (a) Blood samples were obtained from the rats for centrifugation to obtain platelet-rich plasma (PRP). (b) Centrifuge used to obtain PRP. (c) Fluid porcine gelatin combined with human thrombin (Surgiflo hemostatic matrix, Ethicon Inc., New Brunswick, New Jersey), before preparation, combined with PRP. (d) The two components of Surgiflo were mixed to obtain the active compound. (e) Oxidized regenerated cellulose (Surgicel, absorbable hemostatic, Ethicon Inc., New Brunswick, New Jersey). (f) Fibrinogen combined with human thrombin (Beriplast, CSL Behring, Germany).

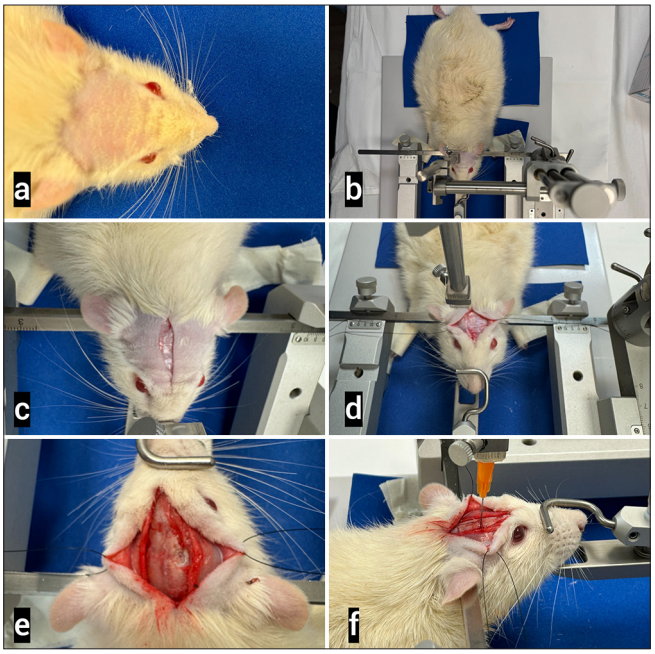

Figure 2: Model for the Transcranial Approach in Animals. (a) The animal, previously anesthetized, was shaved. (b) It was positioned in a prone position and fixed using a stereotaxic system (Stoelting, Illinois, USA) with attachments to both external ear canals and a third fixation at the oral level. Total immobilization was confirmed. (c) A sagittal incision was made on the skin. (d) The periosteum was dissected, and the bilateral flaps were reflected to expose the skull. The sagittal and coronal sutures were observed. (e) After the craniotomy point was marked with the stereotaxic system and coordinates, a trephination hole was done with a diamond drill until the dura mater was exposed. The dura was then opened with a number 11 scalpel blade. (f) Finally, a needle was inserted to a depth of 2 mm to induce bleeding using the stereotaxic system. A randomly assigned hemostatic agent was applied, and the hemostasis time was measured with a stopwatch. Steps (e and f) were repeated on the contralateral side without a hemostatic agent as a control time.

Surgiflo and Beriplast, which need to be prepared on the operating table. On contact with blood, it forms a brown gelatinous substance that aids in clot formation, serving as a hemostatic adjunct in controlling local bleeding. If left in the surgical bed, it will be reabsorbed within

7–14 days, depending mainly on the amount of product and degree of blood saturation. It should not be used in bone foramina, confined bony areas, the spinal cord, or the optic chiasm and nerve. It can expand spontaneously and may exert undue pressure.[13] Its low pH has a bactericidal effect on a broad spectrum of organisms, including both Gram-positive and Gram-negative bacteria, as well as aerobes and anaerobes. This product is approved for various surgical applications, including abdominal, thoracic, neurosurgical, orthopedic, and ENT procedures.[10] A dose of 0.1 cm^3 was used on the basis of a study by Altun (2021), who reported that this quantity of product was effective in rat laminectomies with defects of 7 × 4 mm.[1] Notably, to our knowledge, there are no other studies that standardize the dose of this agent and correlate it with a given extent of tissue damage. This is why we chose this amount of product to cover the parenchymal lesion.

2. Fluid Porcine Gelatin Combined with Human Thrombin (Surgiflo, Hemostatic Matrix, Ethicon Inc., New Brunswick, New Jersey): available as an 8 mL syringe of fluid porcine gelatin, with human thrombin in a powder vial (2,000 IU) mixed with 2 mL of sterile water, forming a single activated component in a syringe with an applicator tip. After the required amount is applied, the excess is irrigated. It has a reabsorption time of 4–6 weeks. This product should also be removed from the site when used around or near bone holes, confined bony areas, the spinal cord, and/or the optic nerve and chiasm, as it may enlarge and cause nerve damage.[13] As with Surgicel, there is no standard dose of Surgiflo, and this is managed in everyday practice by the surgeon, who usually uses the amount of product that stops bleeding without a specific measure. This is why, on the basis of the study of Altun, which is the closest to a reference dose,[1] we used 0.1 mL of Surgiflo.
3. Fibrinogen combined with human thrombin (Beriplast, CSL Behring, Germany): widely used in various neurosurgical procedures, including aneurysm clipping, tumor excision, dural closure to prevent cerebrospinal fluid leakage, neurorrhaphy, and bleeding control during spinal surgery.[5] It consists of 4 vials: the first with fibrinogen and coagulation factor XIII, the second with bovine lung aprotinin, the third with thrombin, and the fourth with calcium chloride dihydrate, totaling 3 mL. The components are mixed in two syringes and administered simultaneously to form the active agent on contact. The fibrinogen concentration in these fibrin sealants is usually approximately 20 g/L, and fibrin clot formation, when mixed with thrombin, takes 2–10 s.[5] The amount applied depends on the surgeon's needs, typically between 0.5 and 3 mL. To the best of our knowledge, this is the least studied hemostatic agent in neurosurgery, both in animal models and in humans. As a reference, in the previously mentioned study, 0.1 mL of fibrin glue was applied to a 7 × 4 mm spinal defect.[1]
4. PRP: This is a fraction of plasma that is obtained from autologous blood after centrifugation. It contains a high concentration of platelets and growth factors that are actively secreted by the platelets. PRP is rich in certain proteins and agents that act on cellular adhesion (such as fibrin, fibronectin, and vitronectin), providing structural support for processes such as cellular migration and tissue growth. PRP has effects on the extracellular matrix and stimulates tissue repair and regeneration.[12] This component was used in a surgical bleeding model in rat livers by Sirieix *et al*.,[16] who combined it with 10% calcium chloride and 1000 U of human thrombin, with or without 400 KUI of aprotinin, to create 0.5 mL of fibrin glue. The plasma units collected in blood banks can be autologous or homologous. This component can be easily obtained through blood sample centrifugation. To the best of our knowledge, this is the first trial that analyzes the topical hemostatic properties of PRP in brain tissue. We chose to use 0.1 mL of PRP since the damaged tissue was smaller than in the previously mentioned study [16], and we followed the protocol used for the other agents used in this experimental trial.

The following groups were established in which the study rats were randomly designated:

- Group 1: Regenerated oxidized cellulose (Surgicel) 0.1 cm^3
- Group 2: Fluid porcine gelatin combined with human thrombin (Surgiflo) 0.1 mL
- Group 3: Fibrinogen combined with human thrombin (Beriplast) 0.1 mL
- Group 4: Surgicel 0.1 cm^3 + PRP
- Group 5: Beriplast 0.1 mL + PRP
- Group 6: Surgiflo 0.1 mL + PRP
- Group 7: PRP 0.1 mL.

In each case, the hemostasis time (defined as the time in seconds between incision and cessation of visible spontaneous bleeding) was measured with a stopwatch, and the number of applications needed to achieve hemostasis was recorded. Any residual hemostatic material was irrigated. The procedure was repeated on the contralateral side of the same animal without the application of any hemostatic agent, which served as a control. Complications and/or adverse reactions during or after surgery were recorded.

Termination

All euthanasia techniques must ensure the absence of pain or distress; the method should be painless and stress-free, facilitating rapid unconsciousness and death.[2] At the end of the procedure, the animal was administered an inhaled anesthetic (sevoflurane), and all vital support was

removed. The animal was exposed to 5% anesthetic until respiratory and circulatory arrest was confirmed. Death was confirmed by physical methods or exsanguination (absence of pulmonary ventilation and heartbeat, associated with the absence of reflexes, pupillary dilation, and mucosal cyanosis due to lack of oxygenation). Both anesthesia induction and euthanasia were carried out by a veterinarian experienced in laboratory animal handling.

Statistical analysis

Longitudinal data analysis was performed through a one-way analysis of variance (ANOVA). Specific comparisons between all of the treatment arms were conducted through ANOVA to evaluate significant differences. The homogeneity of the variances was assessed at this stage. To offer clearer insight into the trends, individual profile plots were created. To establish the specific differences between groups, *post hoc* tests with multiple paired comparisons were used. *t*-tests were used to assess if there was a statistically significant difference between the means of two paired groups. This approach allowed not only an examination of general patterns but also the identification of potential variations in individual responses and differences between treatment groups and negative controls. Values of $P < 0.05$ were considered statistically significant, with 2 standard deviations included in the measurements obtained. All the data are expressed as the means ± standard deviations.

RESULTS

Efficacy evaluation

Hemostasis was achieved after all the hemostatics were applied for 1 minute [Figure 3]. Complete hemostasis was achieved after an average of 1.82 s in the group treated with Beriplast 0.1 mL, making it the fastest hemostatic agent. The Beriplast + PRP group achieved hemostasis in an average of 2.11 s. However, the difference between these two groups was not statistically significant ($P = 0.29$). In comparison to their respective control groups without hemostatic, the difference was statistically significant in both groups ($P < 0.001$). Surgiflo achieved a hemostasis time of 4.52 s, whereas the same product with PRP achieved bleeding cessation in an average of 4.03 s. Compared with the negative control group, the Surgiflo treatment group showed a statistically significant difference ($P < 0.001$). The difference between the Surgiflo + PRP group and its negative control was significant ($P < 0.001$). However, the difference between these two treatment branches was not significant ($P = 0.12$). The Surgicel group achieved hemostasis at an average of 5.74 s, with the difference from the average control time being statistically significant ($P < 0.001$). For the Surgicel + PRP combination, the average coagulation time was 13.99 s. The difference compared with that of the negative control was significant ($P = 0.003$). The difference between these two treatments (with and without PRP) was also significant ($P = 0.01$). Finally, the hemostasis time with only PRP was 6.91 s on average, with the difference from the negative control being significant ($P < 0.001$). The average control time (without hemostatic) was 40.14 s in the 42 animals. Reapplication of the product was not necessary in any case. No complications were recorded during the procedures. The average surgical time was 11.28 min. Compared with the negative control, all the agents resulted in significantly better hemostasis in the same animal. There were no perioperative complications, either in the preparation or application of the hemostatic agents.

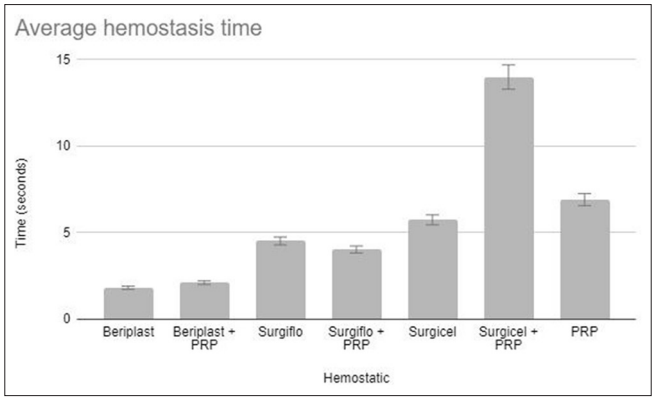

Figure 3: Complete hemostasis was achieved within 1 minute for all the topical agents analyzed. PRP: Platelet-rich plasma

DISCUSSION

As more surgical procedures are performed through minimally invasive incisions, tools that can reduce bleeding by inducing blood coagulation, sealing vessels, or adhering tissues are becoming increasingly important.[15] In general, absorbable hemostatic agents are not administered according to a standardized dosage regimen; instead, the minimal amount of product required to achieve hemostasis is used in daily practice.[7] Ereth *et al*. conducted an experimental study on brain tissue from 228 rats and measured the efficacy and safety of starch-derived hemostatic powder (Arista), oxidized cellulose (Surgicel), microfibrillar collagen (Avitene), and bovine gelatin matrix-bound thrombin (FloSeal), finding excellent results in their application.[6] A limitation of that protocol was that fibrin sealants were not studied despite being the only agents capable of initiating coagulation without involving the patient's coagulation system and showing the highest efficacy in our study. Another limitation is that the doses of each agent were not clearly defined in the study.

Takizawa *et al*. used 16 rabbits to test the hemostatic efficacy of gelatin sponges alone (Gelfoam) and oxidized cellulose alone (Surgicel), both alone and combined with fibrin

adhesive (Bolheal).[17] However, this study was conducted in the vena cava rather than in brain tissue, so it is not directly comparable to neurological tissue but serves as a starting point for studies in more similar models. In this study, gelatin sponges and oxidized cellulose were used either alone or in combination with fibrin glue, and then, a comparison of the hemostatic effects of the four groups was done. The combination of gelatin sponges and fibrin glue had the greatest hemostatic effect;[17] similarly, our study revealed that fibrin adhesives yielded better results.

Sabab *et al*. used 90 rats to study topical hemostatics.[13] Although the primary objective was to analyze the safety and efficacy of chitosan in the rat brain, other hemostatics (such as regenerated oxidized cellulose and porcine gelatin plus human thrombin) were also tested. This study revealed that chitosan has similar or even superior hemostatic properties and lower acute inflammation than conventional hemostatics do, which constitutes a basis for further studies in other biological models. Rajiv *et al*.[11] and Brandenberg *et al*.[3] used animal models with surgical brain injury (sheep with 3 months of recovery and cats with recovery of 6–8 weeks, respectively), in which regenerated oxidized cellulose (Surgicel) and porcine gelatin plus human thrombin (FloSeal) were applied. After the observation period, the authors assessed the extent of the macrophage reaction within the brain tissue. In both studies, there were no significant differences with regard to the macrophage response between these hemostatics. Ereth *et al*. also demonstrated that, in the acute stage (6 h, 12 h, and 3 days), there was no significant inflammatory response to these two hemostatic agents.[6]

Since the active agents are directly involved in the final stages of the coagulation cascade and bypass the initial enzymatic steps, other components of the coagulation cascade may be dysfunctional or scarce without significantly affecting the local hemostatic efficacy of the products.[15] In this study, we confirmed that fibrinogen combined with human thrombin (Beriplast) achieved hemostasis in the shortest amount of time. In fact, it could be a useful adjunct in the presence of antiplatelet and/or anticoagulant therapy, which are increasingly used in the general population.[15] According to the findings of this experimental study and in accordance with other lines of investigation that we analyzed before, we can say that Beriplast is an agent that not only works as a dural sealant but also has been proven to be effective as a hemostatic agent, surpassing other available products. Even though PRP is a cheap derivative from blood centrifugation that can be easily obtained before a surgical procedure, it did not show appropriate hemostatic properties alone or as a cofactor with other hemostatics in this trial. Further randomized clinical trials should be carried out in the future in humans, not only to assess the efficacy of these agents intraoperatively but also to analyze the postoperative morbidity, mortality, length of hospital stay, costs, and many other parameters.

Limitations

Although the administration of each hemostatic agent was randomized for the animal, there was no blinding of the operator due to the nature of the surgical intervention. In addition, measuring visible bleeding cessation is not a precise endpoint for hemostasis because this process is better assessed with imaging studies, such as a CT scan. The doses of the products used in this trial were fixed for the small size of the brain lesion. Further studies using different doses for increasing extents of brain injury should be carried out as an attempt to correlate quantity to extension. The use of a small animal model is another limitation of this study, as there are differences in vascular size, flow, coagulation, and pressure parameters compared with those of humans. The Wistar rat has a heart rate of 300–500 beats/min, hematocrit of 36–54, platelet count of 600×10^3 uL ($\pm 150 \times 10^3$), and systolic blood pressure of approximately 114 ± 2 mmHg. As vital signs in humans significantly differ, the response to hemostatic agents during surgery must also differ. In this study, vital signs were not controlled continuously during the intervention, so the findings were not correlated with these normal physiological variables. Further investigations using other models are needed to confirm these findings, which will serve as a starting point until protocols for standard use in humans are proposed. Future research could focus on the application of these hemostatics in the context of known coagulation disorders or concomitant antiplatelet or anticoagulant therapy. Another limitation of this study is that the survival rate and behavior of the rats were not assessed postoperatively, as in some studies mentioned previously [3,6,11,13], and that pathological studies of the brain were not performed. The assessment of the inflammatory reaction and incidence of infections in brain tissue with the hemostatics studied in this article constitutes a future line of research since heterologous hemostatic products have more or less prolonged degradation times, which entail risks of infection, seizures, and mass effect in the brain parenchyma with the potential to generate complications in the postoperative period, and this was not evaluated in this experimental study. Another future line of investigation would be to observe and analyze the behavior of these animals postoperatively.

CONCLUSION

Reducing the time that a surgeon needs to manage intraoperative bleeding decreases operative times and optimizes human resources. A reduction in postoperative hemorrhage incidence positively impacts annual morbidity and mortality, hospital stay duration, and bed turnover. Understanding the efficacy and safety of different hemostatics will allow surgeons to optimize intraoperative hemostasis, achieving better postoperative results and greater patient safety.

Ethical approval: The research/study approved by the Institutional Review Board at CICUAL- IMTIB, Institutional Committee for the Care and Use of Laboratory Animals, Italian Hospital of Buenos Aires, number 023/24, dated May 21, 2024.
Declaration of patient consent: Patient's consent was not required as there are no patients in this study.
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Conflicts of interest: There are no conflicts of interest.
Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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