An Experimental Study of Histopathologic Effects of Hemostatic Agents Used in Spinal Surgery

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OBJECTIVE: **To evaluate and compare the histopathologic effects of various hemostatic agents used in spinal surgery on an experimental laminectomy model in rats.**

METHODS: **There were 110 rats randomly allocated into 11 groups, including sham, control, AnkaferdBlood Stopper (herbal hemostatic), SeraSeal (agar and bovine factor proteins), FLOSEAL (gelatin granules and thrombin), SURGIFLO (gelatin paste), HELITENE (absorbable collagen), Beriplast (fibrin sealant containing fibrinogen, factor XIII, and thrombin), TISSEEL (fibrin sealant), BLOODCARE (hemostatic powder), and SURGICEL (oxidized cellulose polymer) groups. Hemostatic agents were applied on the epidural region after laminectomy was performed until the identification of dura mater and nerve root. After a follow-up period of 12 weeks, rats were sacrificed, and histologic sections were performed proximal and distal to laminectomy zone. Groups were histopathologically compared in terms of chronic inflammation, fibrosis, and vascularization.**

RESULTS: **There was no difference between groups in terms of acute inflammation ($P = 0.159$). Chronic inflammation was more remarkable in the herbal hemostatic group ($P = 0.036$), and there was severe fibrosis in absorbable collagen hemostatic, fibrin sealant, and powder hemostatic agent groups ($P < 0.001$). Vascularity was more obvious in herbal hemostatic; fibrin sealant; absorbable collagen; fibrin sealant containing fibrinogen, factor XIII, and thrombin; hemostatic powder; and oxidized cellulose polymer groups ($P < 0.001$).**

CONCLUSIONS: **Hemostatic agents can cause notable histopathologic alterations, including inflammation, fibrosis, and vascularity. In this context, flowable hemostats such as gelatin granules and thrombin or gelatin paste seem to provide more promising results in spinal surgery.**

INTRODUCTION

Coagulation has been the mainstay of hemostasis during surgery in the last century. However, problems such as carbonization of the tissue or adhesions to the electrode may be seen as a result of high temperature.[1,2] In this context, hazards associated with thermal injury constitute an important limitation for use of electrocautery in surgical practice. However, failure to achieve hemostasis during surgery can lead to excessive bleeding, which complicates the procedure and causes a substantial risk for morbidity and mortality.[3]

In spinal surgery, these problems can be more obvious, and nerve injury and dural tears may exist as well as increased operative time and need for postoperative blood transfusions.[4,5] If bleeding cannot be controlled by conventional methods, topical hemostatic agents can be used. These topical hemostatic agents are classified into active and passive groups. Passive hemostatic agents consist of collagens, cellulose, and gelatins, and they function by contact activation and enhance aggregation of platelets. Active hemostatic agents, such as fibrin sealants, may include thrombin, and they act biologically on the clotting mechanism.[1,4]

These hemostatic agents may cause significant histopathologic alterations, such as inflammation, adhesion, and fibrosis. These changes may facilitate extradural compression of the nervous structures, and traction of nerve root by epidural adhesion

Key words
- Epidural
- Fibrosis
- Hemostatic
- Histopathology
- Inflammation
- Lumbar
- Vascularization

Abbreviations and Acronyms
ABS: AnkaferdBlood stopper

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and fibrosis not only impairs arterial supply but also may block axoplasmic transport, resulting in painful radiculopathy.[1] Furthermore, the presence of scar tissue in the operative area augments the risks for nerve root lesions and dural tears. To the best of our knowledge, the histopathologic effects of hemostatic agents have not been extensively studied in the medical literature. The objective of the present study was to assess and compare the histopathologic changes attributed to the use of various topical hemostatic agents on the epidural region in an experimental laminectomy model on lumbar spines.

MATERIALS AND METHODS

Study Design

This experimental study was carried out in the experimental research laboratory of our university following approval of the local research ethics committee of experimental animal studies (2014/01-48). In this study, 110 male adult Wistar rats (weighing 400–450 g) were used. Access to food and water was provided ad libitum, and a diurnal cycle for 12:12 hours of light/darkness was provided. All experimental procedures were implemented in accordance with the protocols of the institutional animal care and use committee. Rats were allocated into 11 groups according to the topical hemostatic agent to be applied on the epidural region of the laminectomy site at the level of L4.

Surgical Procedure

The surgical procedure of lumbar laminectomy was performed as described previously in the literature.[5] General anesthesia was induced by application of pentobarbital (10 mL/kg). After shaving the hair around L4, the naked skin was sterilized with povidone-iodine solution. Under aseptic conditions, visualization was provided under a surgical microscope, and a conventional midline approach was used for access to the L4 area. After dissection of the fascia and paraspinal muscles, L4 laminar was removed using a burr. A laminectomy defect of 7 mm × 4 mm was formed using a high-speed drill, and complete exposure to dura mater and the nerve root was provided (Figure 1). The length of dissection of a single block was 6 mm. Nothing was done to the control group (Figure 2). In the sham group, laminectomy was performed (Figure 3), and 0.1 mL saline was administered topically on the epidural region at the site of laminectomy for 5 minutes. Liquid hemostatic agents (AnkaferdBlood stopper [ABS; Ankaferd İlac Kozmetik AS, Istanbul, Turkey], SeraSeal [Wortham Laboratories, Chattanooga, Tennessee, USA], FLOSEAL Hemostatic Matrix [Baxter Healthcare Corporation, Deerfield, Illinois, USA], SURGIFLO Hemostatic Matrix Kit with thrombin [Ethicon Inc., Somerville, New Jersey, USA], Beriplast P Combi-Set 3 mL [Aventis Pharma Limited, Mumbai, India], TISSEEL fibrin sealant [Baxter Healthcare Corporation]) 0.1 mL, powder hemostatic agent (HELITENE [Integra NeuroSciences, Plainsboro, New Jersey, USA]) 0.1 gr, and matrix hemostatic agents (SURGICEL original absorbable hemostat [Ethicon, Inc., Somerville, New Jersey, USA], BLOODCARE Matrix [Life Line plus s.r.o, Brno, Czech Republic]) 0.1 cm^3 were administered topically and covered on the epidural region at the site of laminectomy for 5 minutes. After 5 minutes, the laminectomy sites were irrigated immediately with saline solution to eliminate the surplus relevant hemostatic agent. The wound was closed in layers using the same suture material in each animal. No complications or adverse reactions were encountered during or after surgery.

Hemostatic Agents

Advanced hemostatic agents administered topically in the current study included FLOSEAL Hemostatic Matrix, SURGIFLO Hemostatic Matrix Kit with thrombin, ABS (100 mL), SeraSeal, HELITENE, Beriplast P Combi-Set 3 mL, TISSEEL fibrin sealant, BLOODCARE Matrix, and SURGICEL original absorbable hemostat. After a follow-up period of 12 weeks, rats were sacrificed by intracardiac perfusion of potassium (0.5 mL/100 g body weight). Tissue specimens were resected on the epidural plane proximal and distal to the sites of laminectomy. The section of tissue specimen was performed in the axial direction of the spinal column. After dehydration of tissue specimens, formalin-

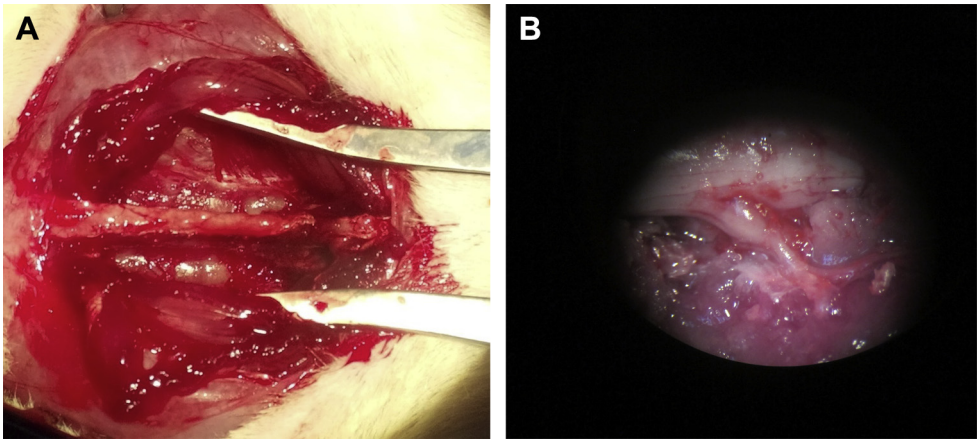

Figure 1. Under a surgical microscope (**A**) after dissection of the fascia and paraspinal muscles, (**B**) a laminectomy defect was formed using a high-speed drill and complete exposure to dura mater and the nerve root.

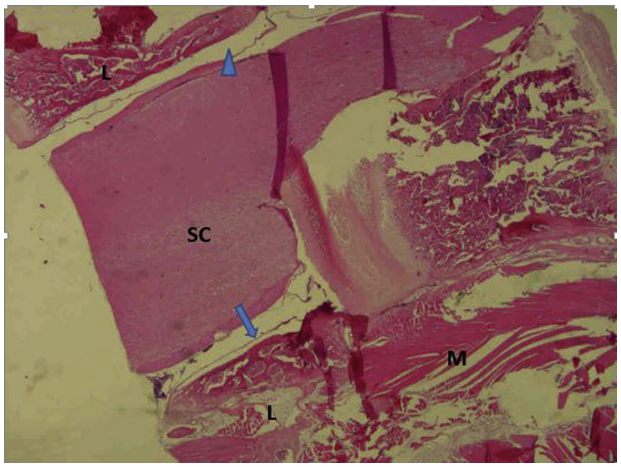

Figure 2. Normal anatomic structures in the control group. *Arrowhead* indicates epidural region. *Arrow* indicates dura mater. SC, spinal cord; L, lamina; M, muscle. (Hematoxylin-eosin, ×40).

fixed paraffin sections were achieved. Each block was cut into sections of 10 mm for allowing optimal visualization of the laminectomy site. Staining was done with hematoxylin-eosin, and all histopathologic examinations were performed by 2 experienced pathologists blinded to the grouping data of experimental animals. Each specimen was examined under the light microscope (Nikon DX-35, Tokyo, Japan) to assess epidural chronic inflammation, and vascularity was assessed using a 4-grade scoring system as follows: 0, none; 1, mild; 2, moderate; 3, severe.[6] Adhesion degrees between dura mater and fibrosis were graded according to the following classification: grade 0, when the dura mater was free of the fibrous tissue; grade 1, when only thin fibrous bands between dura mater and fibrous tissue were observed; grade 2, when continuous adherence was observed but less than two thirds of the laminectomy defect; and grade 3, when fibrous tissue adherence was large, more than two thirds of the laminectomy defect, or extended to the nerve roots.[7]

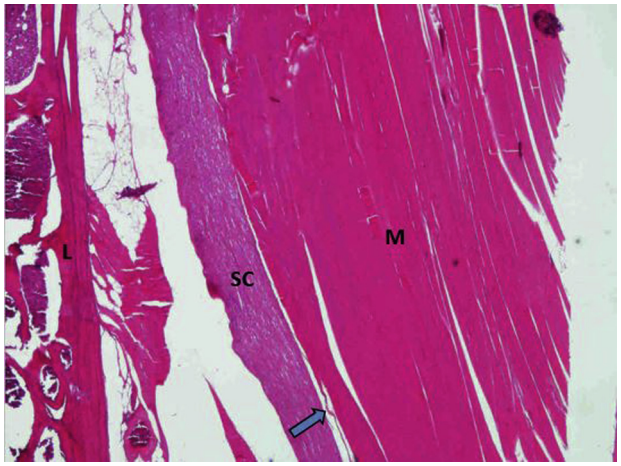

Figure 3. Laminectomy area in the sham group. *Arrow* indicates dura mater. SC, spinal cord; L, lamina; M, muscle. (Hematoxylin-eosin, ×40).

Statistical Analysis

IBM SPSS Statistics version 20.0 software for Windows (IBM Corporation, Armonk, New York, USA) was used for statistical analysis of data. Pearson χ^2 test was used to compare the variables between groups. Confidence interval was 95%, and differences associated with a P value < 0.05 were considered statistically significant.

RESULTS

Comparison of groups receiving different protocols revealed that there were no noteworthy differences between groups with respect to indicators of inflammation (Table 1). In contrast, groups exhibited significant differences in terms of chronic inflammation ($P = 0.036$). The group receiving the herbal hemostatic agent displayed the most severe chronic inflammation (Figures 4 and 5). Rats in control, sham, agar and bovine factor proteins, gelatin granules and thrombin, and gelatin paste and absorbable collagen groups did not demonstrate any findings consistent with chronic inflammation (Table 1).

Groups demonstrated statistically significant differences in terms of adhesion between dura mater and fibrous tissue ($P < 0.001$). The most remarkable adhesion between dura mater and fibrotic changes at the tissue level was identified in absorbable collagen, fibrin sealant, and hemostatic matrix groups. Remarkable adhesion between dura mater and fibrotic changes at the tissue level was identified in herbal hemostatic; agar and bovine factor proteins; and fibrin sealant containing fibrinogen, factor XIII, and thrombin groups. In contrast, no fibrotic changes were observed in the control group (Table 2).

Vascularity was not increased in sham, control, agar and bovine proteins, gelatin granules and thrombin, and gelatin paste groups (Table 2). Mild or moderate increases in vascularity were detected in herbal hemostatic; absorbable collagen; fibrin sealant containing fibrinogen, factor XIII, and thrombin; fibrin sealant; hemostatic powder; and oxidized cellulose polymer groups (Table 2 and Figure 6). Vascularity was considered to be inversely related to scar formation. During experimental interventions, the source of bleeding was epidural veins, and it was difficult to achieve hemostasis by simple irrigation.

DISCUSSION

The goal of the present study was to comparatively evaluate the histopathologic changes encountered after use of hemostatic agents on the epidural region in a laminectomy model. We noted that agar and bovine factor proteins, gelatin granules and thrombin, and gelatin paste did not yield any unfavorable alterations such as inflammation.

Postoperative fibrosis is a physiologic inflammatory phenomenon seen during the healing process of injured tissue. It occurs as

Table 1. Analysis of Acute and Chronic Inflammatory Changes After Application of Topical Hemostatic Agents in Control, Sham, and Study Groups

	Variable					Variable				
	Acute Inflammation					Chronic Inflammation				
Group	None	Mild	Moderate	Severe	*P* Value	None	Mild	Moderate	Severe	*P* Value
Control	10 (100%)	0	0	0	0.159	10 (100%)	0	0	0	0.036*
Sham	10 (100%)	0	0	0		10 (100%)	0	0	0	
Herbal hemostatic†	7 (70%)	2 (20%)	1 (10%)	0		7 (70%)	0	2 (20%)	1 (10%)	
Agar and bovine factor proteins‡	10 (100%)	0	0	0		10 (100%)	0	0	0	
Gelatin granules and thrombin§	10 (100%)	0	0	0		10 (100%)	0	0	0	
Gelatin paste‖	10 (100%)	0	0	0		10 (100%)	0	0	0	
Absorbable collagen¶	10 (100%)	0	0	0		10 (100%)	0	0	0	
Fibrin sealant containing fibrinogen, factor XIII, and thrombin#	10 (100%)	0	0	0		5 (50%)	3 (30%)	2 (20%)	0	
Fibrin sealant**	10 (100%)	0	0	0		8 (80%)	1 (10%)	1 (10%)	0	
Hemostatic powder††	10 (100%)	0	0	0		8 (80%)	1 (10%)	1 (10%)	0	
Oxidized cellulose polymer‡‡	9 (90%)	1 (10%)	0	0		7 (70%)	3 (30%)	0	0	

Control group underwent no procedures at all, whereas sham group received topical isotonic saline after laminectomy.
*Statistically significant.
†AnkaferdBlood Stopper.
‡SeraSeal.
§FLOSEAL.
‖SURGIFLO.
¶HELITENE.
#Beriplast.
**TISSEEL.
††BLOODCARE.
‡‡SURGICEL.

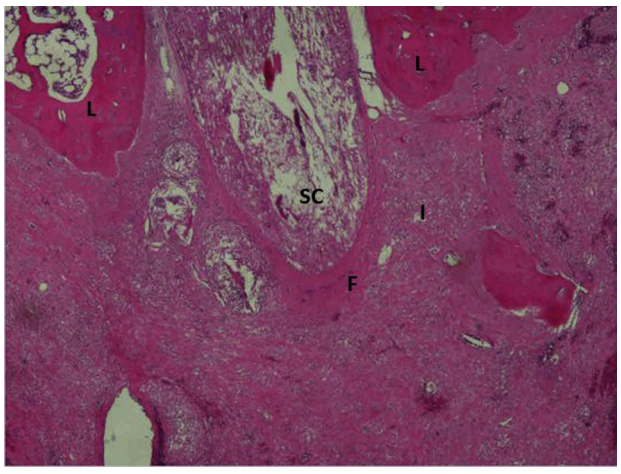

Figure 4. Widespread tissue fibrosis and chronic inflammatory cells between dura mater. SC, spinal cord; F, fibrosis; I, inflammatory cells; L, lamina. (Hematoxylin-eosin, ×40).

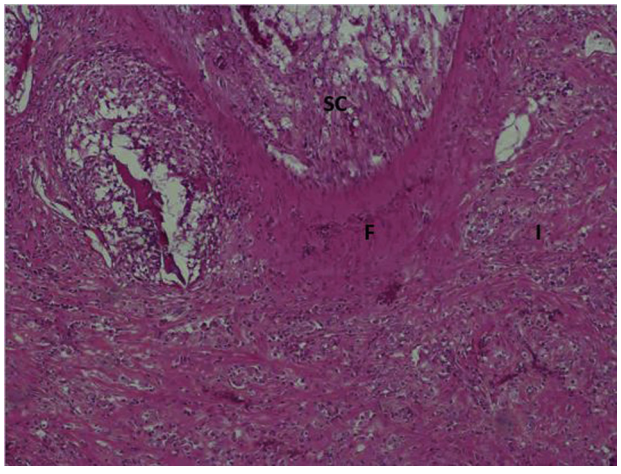

Figure 5. Grade III fibrosis between dura mater. The epidural fibrosis was adhered to the underlying dura mater and spinal cord. SC, spinal cord; F, fibrosis; I, inflammatory cells. (Hematoxylin-eosin, ×40).

Table 2. Analysis of Fibrosis and Vascularity After Application of Topical Hemostatic Agents in Control, Sham, and Study Groups

	Variable					Variable				
	Fibrosis					Vascularity				
Group	None	Mild	Moderate	Severe	*P* Value	None	Mild	Moderate	Severe	*P* Value
Control	10 (100%)	0	0	0	< 0.001*	10 (100%)	0	0	0	< 0.001*
Sham	2 (20%)	3 (30%)	3 (30%)	2 (20%)		10 (100%)	0	0	0	
Herbal hemostatic†	0	1 (10%)	4 (40%)	5 (50%)		7 (70%)	0	3 (30%)	0	
Agar and bovine factor proteins‡	0	1 (10%)	4 (40%)	5 (50%)		10 (100%)	0	0	0	
Gelatin granules and thrombin§	0	3 (30%)	4 (40%)	3 (30%)		10 (100%)	0	0	0	
Gelatin paste‖	0	3 (30%)	4 (40%)	3 (30%)		10 (100%)	0	0	0	
Absorbable collagen¶	0	0	3 (30%)	7 (70%)		9 (90%)	0	1 (10%)	0	
Fibrin sealant containing fibrinogen, factor XIII, and thrombin#	0	0	5 (50%)	5 (50%)		5 (50%)	5 (50%)	0	0	
Fibrin sealant**	0	0	3 (30%)	7 (70%)		5 (50%)	2 (20%)	3 (30%)	0	
Hemostatic powder††	0	0	3 (30%)	7 (70%)		6 (60%)	4 (40%)	0	0	
Oxidized cellulose polymer‡‡	0	0	3 (40%)	7 (70%)		6 (60%)	3 (30%)	1 (10%)	0	

Control group underwent no procedures at all, whereas sham group received topical isotonic saline after laminectomy.
*Statistically significant.
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††BLOODCARE.
‡‡SURGICEL.

a result of the organization of the fibrin matrix in the damaged tissue together with the exudation of fibrinogen and proliferation of fibroblasts.[8,9] Nevertheless, excessive fibrosis in surrounding tissues may cause unintended consequences. In particular, fibrosis around the dura mater and nerve roots would trigger tethering of nerves, neurologic symptoms, and increased risks of nerve injuries after laminectomy of the spine. Furthermore, fibrosis causes a substantial risk of nerve root injury, and reduction of the inflammatory reaction, inhibition of fibroblastic proliferation, and release of exudate may decrease these risks.[9] Therefore, knowledge of the histopathologic reactions associated with hemostatic agents is necessary for selection of the appropriate option during surgery.

Fibrin sealants are not only used for strengthening repairs of elective cerebrospinal fluid fistulas in spinal surgery, but they also provide hemostasis and reduce scar formation.[9] Additional benefits of fibrin sealants include intraoperative hemostasis with reduced postoperative drainage, reduced transfusion requirements, and reduced cost and scar formation.[8,10]

Cekinmez et al.[6] investigated the efficacy of different steroid doses, steroids combined with fibrin sealants, and fibrin sealants alone for limiting epidural fibrosis after spinal procedures in a rat model. There were 100 L4-5 laminectomies performed in 100 Sprague-Dawley rats, and histologic evaluations performed 1, 2, 4, and 6 weeks after the procedure demonstrated comparable frequencies of "epidural fibrosis, inflammation, necrosis and abscess formation."[6] These authors concluded that no treatment arm proved beneficial.[6]

Richards et al.[8] used fibrin sealants with ADCON-L gel (Gliatech, Cleveland, Ohio, USA), a carbohydrate polymer gel shown to inhibit postsurgical adhesions, as a medicated adhesion barrier to reduce posterior spinal epidural adhesions after laminectomies in a sheep model. Laminectomy defects were treated with fibrin sealants alone or ADCON-L gel, or no treatment was performed. Epidural fibrosis and adhesions were assessed 12 weeks later with magnetic resonance imaging, peel-off testing, and histology. These authors concluded that the ADCON-L gel preparation effectively reduced epidural adhesions in this sheep model.[8]

In 2014, Epstein[11] applied TISSEEL in 22 of 39 patients undergoing laminectomy who exhibited increased intraoperative bleeding. Patients undergoing laminectomy who did not demonstrate increased bleeding did not receive TISSEEL. Additionally, Wu et al.[12] assessed 82 consecutive patients undergoing posterior lumbar fusion or posterior lumbar

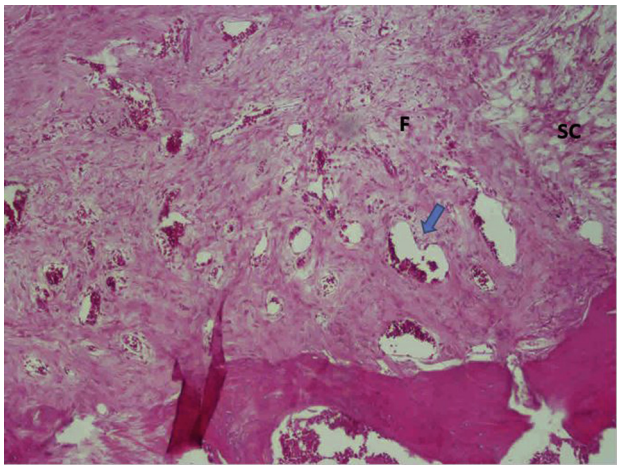

Figure 6. Vascularization (*arrow*) in severe fibrosis between dura mater. SC, spinal cord; F, fibrosis. (Hematoxylin-eosin, ×100).

interbody fusion who were randomly assigned to receive absorbable gelatin sponge versus no sponge. They found that patients receiving the gelatin sponge versus no sponge showed reduced average drainage, reduced perioperative blood transfusion requirements, and reduced length of stay without adverse sequelae.[12]

ABS is a hemostatic agent that consists of a mixture of 5 plants: *Thymus vulgaris*, *Glycyrrhiza glabra*, *Vitis vinifera*, *Alpinia officinarum*, and *Urtica dioica*. Each of these plants has effects on endothelial cells, blood cells, angiogenesis, cell proliferation, vascular dynamics, and cell mediators.[13] The main mechanism of ABS involves the formation of encapsulated protein bonds, which are the foci of erythrocyte aggregation. ABS has been successfully used in many clinical cases as a hemostatic agent.[13] ABS can be a safe and promising hemostatic agent in neurosurgery. Once its advantages and disadvantages are documented and clarified, ABS can achieve worldwide popularity beyond its local use.

Commonly used gelatin-thrombin–based flowable advanced topical hemostatic agents offer important advantages in surgery because they can conform to wound contours and fill deep lesions.[2,14] These products have been labeled as hemostatic matrices and exhibit passive and active mechanisms of action in the blood-clotting cascade via contact activation and active biologic agents, including thrombin.[14]

The present study yielded important clinical clues for selection of suitable hemostatic agents in spinal surgery. First, we noted that inflammation was similar in all groups receiving various agents. These findings indicate that the inflammatory process, likely to be linked with fibrosis or vascularity, is more likely to be shaped in the chronic phase. Therefore, efforts must be made to modify and attenuate the chronic inflammation to accomplish more favorable clinical outcomes. Second, agar and bovine factor proteins, gelatin granules with thrombin, and gelatin paste did not result in either remarkable chronic inflammatory changes or fibrosis. Moreover, vascularity was similar with sham and control groups for these 3 hemostatic agents. Consequently, we advocate the use of these 3 hemostatic agents during spinal surgery in a laminectomy model in rats because they yielded the most favorable histopathologic results.

During surgery, advanced hemostatic agents possess advantages, such as diminution of blood loss, reduction of the need for blood transfusion, avoidance of the need for systemic hemostatic drugs, and shorter duration of stay in the operating room.[15] These benefits can potentially reduce length of stay in the hospital and decrease the cost of care. It has been postulated that clinical efficacy of an advanced flowable hemostatic matrix compared with a nonflowable topical hemostat (e.g., Gelfoam or SURGICEL) was associated with a more significant reduction in time to hemostasis and greater control of bleeding by reducing patient blood loss.[16,17]

None of the hemostasis materials available for neurosurgery, such as gelatins, collagens, oxidized cellulosis, fibrin, thrombin, polysaccharides, and hydrogel-based hemostats or combinations of the aforementioned materials, is 100% complication-free, and they may cause swelling or other histopathologic changes when left in situ. Swelling in a confined space such as the spinal canal may be dangerous because vital neural structures may be compromised.[18] Richter et al.[19] reported that ADCON-L gel provided no additional benefit in terms of scar formation for patients who underwent 1-level lumbar microdiscectomy.

Consistent with these data, results of the present study indicated that flowable hemostatic matrix resulted in more acceptable histopathologic changes compared with nonflowable hemostatic matrix. Therefore, along with individualized and careful assessment of each patient, choice of an active flowable hemostatic matrix can be a more effective tool to address a broad range of active bleeding in spinal surgery. This hemostatic matrix is especially important in spinal surgery because visualization is critical to efficient and successful surgery. Despite the widespread use of advanced hemostatic matrices in surgery, trials focusing on comparing a variety of hemostatic agents have been limited. We hope that our results will provide new insights for rational use of hemostatic agents during spinal surgery. Hemostatic agents can offer additional advantages for the surgeon particularly during procedures around the nerve root.

The main limitations of this study are experimental design and challenges in extrapolation of our data to humans. Other limitations are lack of information on the amount of bleeding in different groups and variability of pressure during application of hemostatic agents. Although maximal effort was expended to have clear-cut cross sections and identical histologic views, variability may have occurred between groups. Further randomized, multicenter trials on larger series are necessary to elucidate the histopathologic impact of hemostatic agents used in spinal surgery.

CONCLUSIONS

The results of the present study show that hemostatic agents can cause notable histopathologic alterations, such as inflammation, fibrosis, and vascularity. In this context, flowable hemostats, such as gelatin granules with thrombin or gelatin paste, seem to provide more promising results in spinal surgery.

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