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Histopathological Evaluation of Liver Tissue Post-Treatment with Hemostatic Agents in Hyperfibrinolysis-Induced Injury: A Comparative Study

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ABSTRACT

Liver trauma complicated by hyperfibrinolysis leads to uncontrolled hemorrhage and systemic coagulopathy, posing significant challenges in clinical management. **Objective:** To analyze histopathological and clinical changes in hepatic tissue after using hemostatic agents TXA, OCR, and Surgiflo to examine volume of blood loss, duration of blood loss, tissue healing, fibrosis, and inflammation. **Methods:** A total of 48 rabbits were systematically assigned to four distinct cohorts placing 12 rabbits in each group: Control, Tranexamic Acid (TXA), Oxidized Regenerated Cellulose (ORC), and Surgiflo. Uniform hepatic injuries were surgically induced in all liver specimens. After that, each cohort had the prescribed course of treatment. Time to hemostasis, blood loss volume, D-dimer levels, survival rate, and liver tissue histology were the primary outcomes that were measured. **Results:** Out of all the groups, Surgiflo had the quickest hemostasis and the least amount of blood loss. The Surgiflo and ORC groups showed better tissue healing, with less fibrosis and mild inflammation, according to histological analysis. The TXA and Control groups, on the other hand, had slower tissue healing and more infiltration of inflammatory cells. **Conclusions:** Surgiflo was found to be the most successful treatment for liver damage with hyperfibrinolysis based on both clinical and histological results. The outcomes validate its application as a dependable choice for reducing hemorrhage and encouraging tissue repair in cases of complicated liver damage.

INTRODUCTION

Because of the liver's intricate vascular supply and significant bleeding risk, liver trauma poses a significant clinical problem. Hyperfibrinolysis, a disorder in which blood clots degrade excessively rapidly, is a frequent consequence that raises the risk of death and causes severe bleeding [1]. This disorder frequently results from decreased liver synthesis of important clotting and antifibrinolysis proteins, including Thrombin-Activatable Fibrinolysis Inhibitor (TAFI) and alpha-2 antiplasmin [2]. Liver regeneration is a unique and complex physiological process governed by the concept of the "hepatostat," which ensures that liver size and function are tightly regulated after injury or partial resection. According to Michalopoulos in 2017, this regulatory mechanism maintains a balance between hepatocyte proliferation and apoptosis, playing a critical role in preserving normal liver tissue architecture and function [3]. Building on this intrinsic regenerative capacity, liver tissue engineering has made significant strides in recent years. Mazza *et al.*, in 2018 highlighted various advancements in the field,

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including scaffold-based systems and bioengineered liver constructs that offer promising alternatives for liver transplantation, especially in the context of increasing organ shortages [4]. However, emerging environmental concerns such as microplastic contamination present new challenges for liver health. In a groundbreaking study, Horvatits *et al.*, in 2022 reported the presence of microplastics in cirrhotic liver tissues, suggesting a possible link between environmental pollutants and chronic liver disease progression [5]. These findings emphasize the need for further investigation into how external factors like microplastics may impair hepatic regeneration and compromise liver tissue integrity, particularly in individuals with pre-existing liver conditions. By creating a physical mesh that encourages platelet adhesion and clot formation, Oxidized Regenerated Cellulose (ORC) aids in stopping bleeding [6]. An antifibrinolytic medication called Tranexamic Acid (TXA) stops fibrin from breaking down by preventing plasminogen from being activated. It is frequently used to lessen blood loss during orthopedic, cardiac, and liver surgeries [7]. Effective bleeding control requires the early use of medications such as thrombin-based medicines, ORC, and TXA [8]. Though their functions in hemostasis are well known, it is unclear how they affect the healing of liver tissue. After therapy, analyzing tissue samples can provide important information about liver cell repair, scar tissue (fibrosis), and inflammation all of which are important components of long-term healing [9].

This study aimed to assess the clinical performance and tissue effects of different hemostatic agents in a rabbit model of liver injury with hyperfibrinolysis. The goal is to determine which treatments best promote healing while minimizing harmful tissue responses.

METHODS

This randomized experimental study involved 48 healthy adult rabbits, each weighing between 2.0 and 2.5 kg. Ethical approval was obtained from the Institutional Animal Care and Use Committee. The rabbits were randomly divided into four treatment groups, with 12 animals in each group.

Group-Control: No hemostatic agent applied post-liver injury

Group-TXA: Treated with Tranexamic Acid

Group-OCR: Treated with Oxidized Regenerated Cellulose

Group-Surgiflo: Treated with Surgiflo Hemostatic Matrix

Surgical Procedure and Hemostatic Intervention

Following overnight fasting, rabbits were anesthetized using intramuscular xylazine (5 mg/kg) and ketamine (35 mg/kg). A midline laparotomy was performed under sterile conditions. A standardized linear abrasion (~2 × 1 cm) was made on the left liver lobe using a scalpel to induce moderate bleeding.

Group-TXA received a local application of TXA (100 mg/kg body weight, dissolved in 2 mL normal saline) directly on the wound surface immediately post-injury.

Group-OCR received a sterile sheet of oxidized regenerated cellulose, cut to the abrasion size and placed directly on the bleeding surface.

Group-Surgiflo was treated using Surgiflo hemostatic matrix (Baxter), prepared as per manufacturer instructions and applied topically to the bleeding site.

Group-Control did not receive any hemostatic agent.

All interventions were applied immediately post-injury, and bleeding was monitored continuously for analysis.

Evaluation of Hemostatic Parameters Time to Hemostasis (TTH)

Measured in seconds from the moment of agent application to visible cessation of bleeding.

Total Blood Loss (TBL)

Estimated using pre-weighed gauze pads and subtracting the dry weight after saturation with blood, adjusted for density (g = mL).

Fibrinolytic Activity

Blood samples were collected via marginal ear vein at 1 hour post-treatment. Plasma D-dimer and plasminogen levels were analyzed using commercial ELISA kits (Rabbit D2D ELISA Kit, United Kingdom).

Histopathological Assessment

Liver tissue samples from all groups were collected on Day 15 post-treatment, fixed in 10% neutral buffered formalin, embedded in paraffin, and sectioned at 5 µm. Slides were stained with Hematoxylin and Eosin (H&E) for general morphology and Masson's Trichrome for collagen/fibrosis. Microscopy was performed at 40× and 100× magnifications, with scale bars included in figure legends. Photomicrographs were annotated with arrows indicating fibrosis, inflammation, and regenerative foci. A semi-quantitative scoring system was used to evaluate key parameters.

Table 1: Standard Values of Libido

Variables	Score 0	Score 1	Score 2	Score 3
Inflammation	None	Mild	Moderate	Severe
Fibrosis	None	Focal	Moderate	Extensive
Hepatocyte Regeneration	Absent	Limited	Moderate	Marked

Note: Scoring was performed independently by two blinded histopathologists. The mean scores from both observers were used for final analysis. Histological evaluation was limited to Day 15 post-treatment. The lack of multiple time points is acknowledged as a study limitation. A follow-up study involving time points on Day 3, 7, and 30 is recommended to assess dynamic healing responses

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Survival Monitoring

All animals were monitored for 72 hours post-intervention for mortality, pain, and distress. Survival rates were recorded and compared among groups. Data were analyzed using GraphPad Prism v9.0 (GraphPad Software, USA). One-way ANOVA was used for intergroup comparisons of TTH, TBL, fibrinolytic markers, and histopathology scores. Tukey's post hoc test was applied to correct for multiple comparisons. Results were expressed as mean ± standard deviation (SD). A p-value < 0.05 was considered statistically significant. Significant differences between groups are indicated in tables and figure legends using superscript letters.

RESULTS

Time to Hemostasis (TTH)

The time to achieve hemostasis varied significantly among the groups ($p < 0.05$). Surgiflo exhibited the shortest TTH, indicating its superior hemostatic efficacy (Table-2). Oxidized Regenerated Cellulose (OCR) also performed well, followed by Tranexamic Acid (TXA). The control group recorded the longest bleeding duration, emphasizing the importance of hemostatic intervention in uncontrolled hemorrhage

Table 2: Time to Hemostasis (TTH) in Rabbits

Groups	TTH (minutes) / Mean ± SD
Control	8.5 ± 1.2^{a}
Group-TXA	5.3 ± 1.0^{b}
Group-OCR	4.8 ± 0.9^{bc}
Group-Surgiflo	3.6 ± 0.8^{c}

Means within a column with different superscripts (a–c) differ significantly at $p < 0.05$.

Total Blood Loss (TBL)

Significant differences in total blood loss were observed between the groups ($p < 0.05$). Surgiflo and OCR groups experienced the least blood loss, highlighting their effective bleeding control (Table 3). The TXA group had higher blood loss compared to Surgiflo and OCR, but significantly less than the control.

Table 3: Total Blood Loss (TBL) in Rabbits

Groups	TBL (mL) / Mean ± SD
Control	12.1 ± 1.8^{a}
Group-TXA	7.6 ± 1.4^{b}
Group-OCR	6.9 ± 1.2^{bc}
Group-Surgiflo	5.4 ± 1.0^{c}

Means with different superscripts differ significantly at $p < 0.05$.

Fibrinolytic Activity (D-dimer Levels)

D-dimer levels, indicative of fibrinolytic activity, were highest in the control group, suggesting excessive clot breakdown. All treatment groups showed significant reduction in D-dimer levels ($p < 0.05$), with Surgiflo demonstrating the greatest suppression of fibrinolysis (Table-4).

Table 4: Fibrinolytic Activity (D-dimer Levels) in rabbits

Groups	D-dimer (ng/mL) / Mean ± SD
Control	320 ± 25^{a}
Group-TXA	210 ± 20^{b}
Group-OCR	190 ± 18^{bc}
Group-Surgiflo	170 ± 15^{c}

Different superscripts indicate significant differences at $p < 0.05$.

Survival Rate

The 72-hour post-treatment survival rate was significantly higher in all treated groups compared to the control. Surgiflo showed the highest survival rate, followed by OCR and TXA ($p < 0.05$) (Table-5).

Table 5: Survival Rate in rabbits

Groups	72-Hour Survival Rate (%)
Control	58^{a}
Group-TXA	75^{b}
Group-OCR	83^{bc}
Group-Surgiflo	92^{c}

Groups with different superscripts differ significantly at $p < 0.05$.

Histopathological Evaluation of Liver Tissue (Day 15 Post-Treatment)

Surgiflo Group

Histopathological examination of the Surgiflo-treated liver revealed organized hepatocyte structure, minimal inflammatory infiltration, and moderate fibrosis indicating effective clot stabilization and tissue healing without excessive scarring (Figure 1). No evidence of necrosis or persistent hemorrhage was observed.

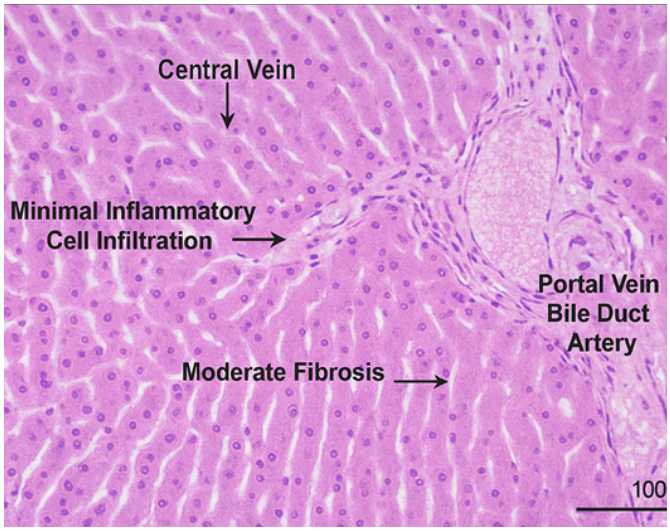

Figure 1: Histopathological section of rabbit liver tissue stained with HandE, 40× magnification, 15 days post-treatment with Surgiflo

The image showed:
Central Vein: Located centrally with surrounding radial arrangement of hepatocyte cords.
Minimal Inflammatory Cell Infiltration: Scattered

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lymphocytes present near sinusoidal spaces.
Moderate Fibrosis: Detected in the portal area, indicating organized tissue remodeling.
Portal Triad: Comprising Portal Vein, Bile Duct, and Hepatic Artery clearly demarcated.
Hematoxylin and eosin (HandE) stain; scale bar = 100 µm.

OCR Group

OCR-treated liver samples demonstrated stable clot formation and largely preserved hepatocyte architecture. Mild fibrosis and a minimal inflammatory response were noted, suggesting good hemostatic and regenerative outcomes (Figure 2). OCR also showed residual hemostatic material, expected due to its slow resorption.

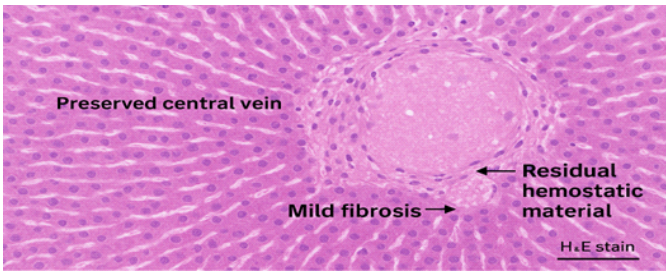

Figure 2: Liver tissue section from rabbit treated with Oxidized Regenerated Cellulose (OCR), HandE staining at 40×magnification

Preserved Architecture: Hepatocytes arranged in cords with maintained sinusoidal pattern.
Mild Fibrosis: Located around the clot and portal region.
Residual Hemostatic Material: Still visible due to slow degradation of OCR.
Minimal Inflammatory Infiltration: Sparse immune cells suggesting resolution phase of healing.
Hematoxylin and eosin (HandE) stain; scale bar = 100 µm.

TXA Group

TXA-treated liver sections exhibited moderate inflammation and mild fibrosis, with some signs of ongoing tissue repair (Figure 3). Hepatocyte organization was generally maintained, with no visible necrosis or hemorrhage

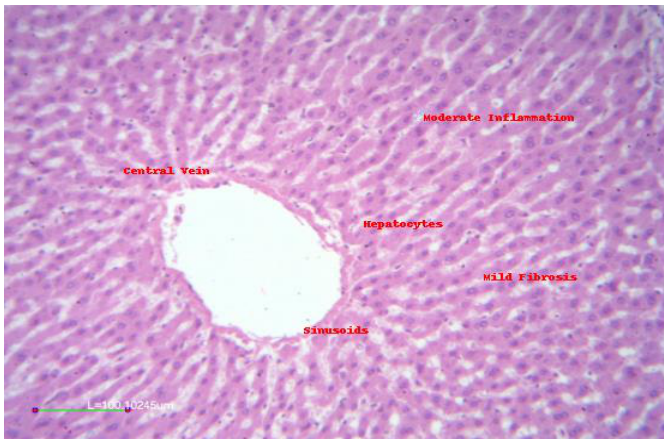

Figure 3: Liver tissue post-TXA treatment showing mild fibrosis and moderate inflammation

Control Group

The control group displayed severe inflammatory infiltration, disorganized hepatocytes, delayed fibrosis, and inconsistent clot formation (Figure 4). These findings confirm poor healing and prolonged hemorrhage in the absence of hemostatic agents.

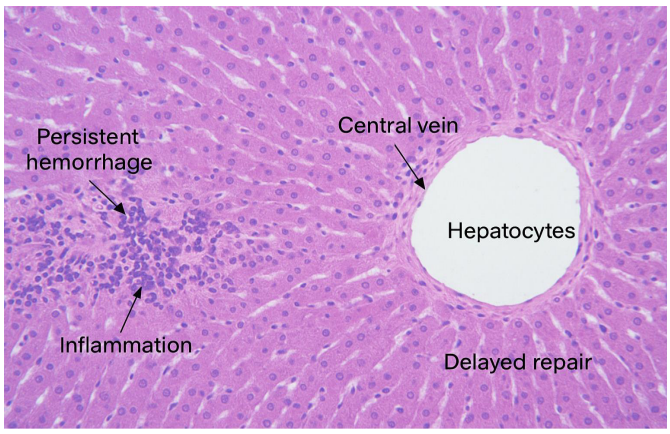

Figure 4: The Control Group's Liver Tissue Displayed Delayed Healing, Inflammation, And Ongoing Bleeding

Histological Interpretation Summary

The histopathological slide of liver tissue treated with Oxidized Regenerated Cellulose (OCR) after fifteen days post-biopsy reveals key changes indicative of tissue healing and response to the applied hemostatic agent.

Clot Stability and Residual Hemostatic Material

Histological sections revealed that Oxidized Regenerated Cellulose (OCR) and Surgiflo facilitated stable clot formation, with possible presence of residual hemostatic materials, particularly OCR, due to its slow resorption characteristics. At the site of the damage, these materials helped to create a scaffold and provide mechanical hemostasis.

Tissue Healing and Regeneration

Hepatocyte structure was mostly intact in the liver tissue of the Surgiflo and ORC-treated groups. Hepatocyte swelling ranged from mild to substantial, suggesting continued regeneration. The hepatic sinusoids and central veins seemed normal, indicating sustained blood flow and conducive healing circumstances.

Inflammatory Response

The Surgiflo and ORC groups' tissue samples displayed a little infiltration of macrophages and lymphocytes, indicating a managed inflammatory response and continuous tissue healing. The control group showed significant inflammatory infiltration and bleeding, suggesting delayed healing, whereas the TXA group showed a mild degree of inflammation.

Fibrosis Development

Localized at the wound margins as a result of fibroblast activation and collagen deposition, fibrosis was mild in the Surgiflo group and slightly higher in OCR-treated samples.

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While the control group displayed uneven or undeveloped fibrous tissue, indicating inadequate repair, the TXA group demonstrated restricted fibrotic growth.

Table 6: Histopathological Assessment Summary

Variables	Control	TXA	OCR	Surgiflo
Clot Stability	Poor	Moderate	Good	Excellent
Tissue Healing	Delayed	Moderate	Good	Excellent
Inflammation	Severe	Moderate	Mild	Minimal
Fibrosis	Disorganized	Minimal	Mild–Moderate	Moderate

DISCUSSION

In both humans and animals, blood is vital for defending the body against chemical and physical damage. Red blood cells, white blood cells, platelets, and plasma make up its composition [10]. Thrombin is formed during coagulation by a sequence of enzyme-driven processes. After that, thrombin converts fibrinogen to fibrin, forming a solid clot that aids in halting the bleeding [11]. To anesthetize rabbits effectively, ketamine hydrochloride (100 mg per rabbit) and xylazine hydrochloride (11.5 mg per rabbit) were used. Adequate sedation, pain alleviation, and muscular relaxation were all made possible by this combination. These findings parallel those of Oguntoye and Oke, who used 50 mg/kg of ketamine and 5 mg/kg of xylazine, as well as those of other researchers who used 35 mg/kg of ketamine and 5 mg/kg of xylazine [12, 13]. In line with earlier research, the anesthesia lasted 36–43 minutes [14]. In this investigation, rabbits treated with ORC and TXA saw considerably less blood loss (mg/min) on average than untreated controls ($P < 0.05$). Similar results utilizing ORC in rabbit models were reported by Guo *et al.*, and others [15, 16]. Numerous studies have also been conducted on TXA's function in regulating bleeding and fibrinolysis [17]. With oral dosages ranging from 10–20 mg/kg, three–four times a day, it is frequently used to treat menorrhagia [18]. The reported maximum oral TXA concentration is 13.83–16.41 µg/ml [19]. The current findings align with previous work on TXA and ORC in surgical hemostasis [20]. In this study, both ORC and TXA significantly influenced bleeding and clotting times ($P < 0.05$), similar to results from heart valve surgery patients [15]. Grottke *et al.*, in 2022 conducted a comprehensive review highlighting the clinical implications of NOAC use in trauma patients, emphasizing the difficulties associated with bleeding management, the limited availability of specific reversal agents, and the lack of standardized protocols in emergency care settings [21]. They reduce intraoperative blood loss, potentially minimizing transfusion needs. TXA has also been effective in cesarean sections, without contributing to thrombotic events [22]. A Nigerian controlled trial examined TXA's effect on fibrinolysis in high-risk postpartum women [23]. TXA's effects on platelets were assessed independently of surgical confounders. This study revealed that ORC achieved hemostasis faster than TXA, particularly in minor liver abrasions. ORC controlled bleeding in under 90 seconds (VIBe SCALE grades 1–2), while TXA averaged 256 seconds. This supports findings from previous rabbit liver injury models [24]. The management of major bleeding and coagulopathy in trauma patients is a critical component of emergency care, directly influencing morbidity and mortality outcomes. According to the European guideline on the management of major bleeding and coagulopathy following trauma (fifth edition), early and aggressive intervention is essential, including timely hemostatic resuscitation, the use of goal-directed transfusion strategies, and incorporation of pharmacological agents to support coagulation [25]. Among these agents, tranexamic acid (TXA) has emerged as a key therapeutic option. The landmark CRASH-2 trial provided robust evidence that early administration of TXA (within 3 hours of injury) significantly reduces the risk of death due to bleeding without increasing the rate of vascular occlusive events, making it a safe and effective addition to trauma protocols worldwide [26]. Together, these guidelines and clinical trial findings underscore the importance of evidence-based, protocol-driven approaches in trauma settings to enhance survival and minimize complications from hemorrhage. Selecting the appropriate hemostatic agent is crucial. While TXA is effective for mild bleeding, passive agents like ORC are preferable for moderate hemorrhages [27].

CONCLUSION

According to histological research, ORC and Surgiflo were superior at halting bleeding, lowering inflammation, and promoting tissue repair. The control group exhibited poor healing with persistent bleeding and inflammation, whereas TXA had moderate effects.

Authors Contribution

Conceptualization: HAM, ABK, MCM, MT, TS
Methodology: HAM, ABK, MCM, MT, TS
Formal analysis: HAM, ABK, MCM, MT, TS
Writing, review and editing: HAM, ABK, MCM, MT, TS

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

All the authors declare no conflict of interest.

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