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ORIGINAL ARTICLE

Effect of Tranexamic Acid Loaded Nanoparticles on Intra-Abdominal Adhesion Formation Following Laparotomy in Rats

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Tranexamic Acid Nanoparticles and Intra-Abdominal Adhesion in Rats

Abstract

Intra-abdominal adhesions frequently arise as a complication following abdominal surgeries. These adhesions lead to internal scarring as a result of damage to abdominal organs, including the peritoneum. This research explores the effects of a Nano-formulated version of tranexamic acid on intra-abdominal adhesions in rats, utilizing both microscopic and macroscopic analysis. A total of thirty adult male Wistar rats (weighing between 300 and 350 grams) were randomly divided into three treatment groups: a control group, a group receiving Nano-drug tranexamic acid (50 mg/kg), and a group receiving standard tranexamic acid (50 mg/kg). Anesthesia was administered via intramuscular injections of 10% ketamine (50 mg/kg) and 2% xylazine (5 mg/kg) as per established guidelines. Adhesion was induced in all subjects by making incisions in the abdominal wall. On days 14 and 28 post-surgery, all rats underwent a second laparotomy, during which the extent of intra-abdominal adhesions was evaluated through both macroscopic and microscopic inspections. The macroscopic evaluation indicated a marked reduction in the formation of adhesion bands within both the Nano-drug and standard drug treatment groups when compared to the control group ($P < 0.05$). The Nano-drug treatment group exhibited the least amount of adhesion, whereas the control group showed the greatest incidence. Microscopic examination of pathological slides from the adhesion sites revealed that levels of inflammation and fibrotic tissue development were significantly reduced in both treatment groups versus the control group ($P < 0.05$). The Nano-drug group exhibited the lowest levels of inflammation and fibrotic tissue, while the highest levels were recorded in the control group.

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Introduction

Intra-abdominal adhesions rank among the most common complications after abdominal surgeries, impacting more than 90% of individuals who undergo these procedures, with dire cases potentially resulting in death (1). Adhesions form when fibrous tissue connects abdominal organs to one another or to the abdominal wall. Although they often present without symptoms, these adhesions can lead to a condition known as adhesive disease. Standard laboratory tests and imaging methods usually fail to provide a definitive diagnosis for adhesive disease, which may lead to long-lasting issues, such as intermittent obstruction in the small intestine. While abdominal surgery is recognized as the main cause of adhesive disease, factors such as infections, inflammation, and radiation therapy can also play a role. Despite considerable investigation, the exact mechanisms behind adhesion formation remain elusive. It is believed that the development of adhesions occurs in three phases: the destruction and rupture of the mesothelial surface, the coagulation of fibrin, and the subsequent inflammatory response. Symptoms associated with adhesive disease can include persistent bloating, abdominal pain, constipation or increased bowel frequency, nausea, indicators of intestinal obstruction, and rectal bleeding (2).

Avoiding internal abdominal adhesions can be achieved through three primary approaches: reducing damage to the peritoneum during surgical procedures, using medication to control the production and breakdown of fibrin, and implementing physical barriers to stop organ adhesion within the abdomen (3, 4).

Tranexamic acid, which resembles lysine in structure, acts as a competitive inhibitor for the conversion of plasminogen into plasmin. This action helps prevent the breakdown of fibrin clots and provides anti-fibrinolytic effects. Its main applications are to avert significant bleeding and lessen the necessity for blood transfusions, while also decreasing inflammatory responses by blocking plasminogen activation (5–7).

In recent times, the use of nanoparticles has increased significantly, leading to the development of various medications incorporated within nanomaterial frameworks. These nanoparticles, defined by their tiny dimensions (ranging from 1 to 100 nanometers), high reactivity, and adaptable surface properties, can be delivered through multiple routes, including topical applications, subcutaneous injections, oral consumption, direct injections, and inhalation. The pathways for excreting these particles differ based on their size, method of administration, shape, and surface features, with removal generally occurring through the kidneys, liver, or lungs (8, 9).

Materials and Methods

This investigation took place at the Faculty of Specialized Veterinary Sciences, Science and Research Branch, Tehran, Iran, with the endorsement of the Ethics Committee of Islamic Azad University Science and Research Branch (Reference No. 1400348).

Surgical Procedure

In this experiment, a total of 30 male Wistar rats, approximately 4 months old and weighing 300-350 grams, were used. The rats were randomly divided into three equal groups: the first group received nano-drug tranexamic acid (50 mg/kg), the second group was treated with standard tranexamic acid (50 mg/kg), and the third group served as a control, receiving normal saline.

Before the surgical procedure, the rats were fasted overnight. On the day of surgery, they were anesthetized with an intramuscular injection of 10% ketamine (50 mg/kg) and 2% xylazine (5 mg/kg). For surgical preparation, the midline abdominal area was thoroughly cleansed using 2.5% povidone-iodine.

A 3-cm incision was carefully made along the midline, and upon entering the peritoneal cavity, three 2-cm longitudinal incisions were made on the right side of the abdominal wall (inner surface) using a No. 4 surgical blade to create standard adhesions. Additionally, 2 × 2 cm sections were excised from the inner surface of the left abdominal wall using surgical scissors to promote intra-abdominal adhesion formation.

The abdominal opening was closed using 3-0 absorbable monofilament Vicryl sutures in a simple interrupted pattern with 1 cm spacing. The fascia and midline muscles were approximated with 2-0 absorbable monofilament Vicryl sutures, while the skin was closed with 3-0 non-absorbable monofilament nylon sutures. Throughout the procedure, the rats' body temperature was maintained between 36°C and 38°C using a heat lamp.

Treatments

A total of 30 male Wistar rats were randomly divided into three equal groups, and initial surgical procedures were performed. The treatment phase lasted for 28 days, beginning on the day of lesion creation. In the first group, after adhesion induction, nano-formulated tranexamic acid (50 mg/kg) was administered intraperitoneally. The second group received standard tranexamic acid (50 mg/kg) intraperitoneally following adhesion induction. The third

group, serving as the control, received intraperitoneal normal saline solution after adhesion induction.

Macroscopic Evaluation

On postoperative days 14 and 28, relaparotomies were performed to assess adhesions. The same surgeon performed all evaluations and classified the adhesions according to established criteria. As shown in Table 1, each adhesion's severity was individually evaluated and comparatively analyzed (10).

Table 1. Scoring and macroscopic categorization of abdominal adhesions in rats (10).

Score	Description
0	No adhesive bands
1	One thin, non-vascular, easily removable
2	Two non-vascular, easily removable
3	Three non-vascular, easily removable
4	More than 3 non-vascular, easily removable

Histopathological Evaluation

On postoperative days 14 and 28, tissue samples were collected from adhesion sites and fixed in 10% neutral formalin solution for 48 hours. The samples were then sectioned at 4 µm thickness and stained using Harris's hematoxylin and alcoholic eosin for histopathological assessment. Prepared slides were examined using light microscopy at 100× magnification (11, 12).

Data Analysis

Each rat and sample was assigned a unique identifier, with comprehensive checklists recording all relevant variables, including adhesion extent and histopathological features. Data were analyzed using GraphPad Prism version 9.00 (GraphPad Software, San Diego, CA) employing the Kruskal-Wallis test. Statistical significance was set at $P < 0.05$, enabling quantitative analysis of qualitative parameters such as adhesion severity, fibrosis, and inflammation levels.

Results

Macroscopic Examination

Macroscopic evaluation on days 14 and 28 revealed no abdominal fluid accumulation in any of the study groups. Throughout the treatment period, no rats exhibited signs of infection or intestinal obstruction. Fourteen-day postoperative analysis demonstrated significantly reduced abdominal adhesion formation in the nano-tranexamic acid group (50 mg/kg) compared to controls ($P < 0.05$), with the control group showing maximal adhesion prevalence (Figures 1 and 2).

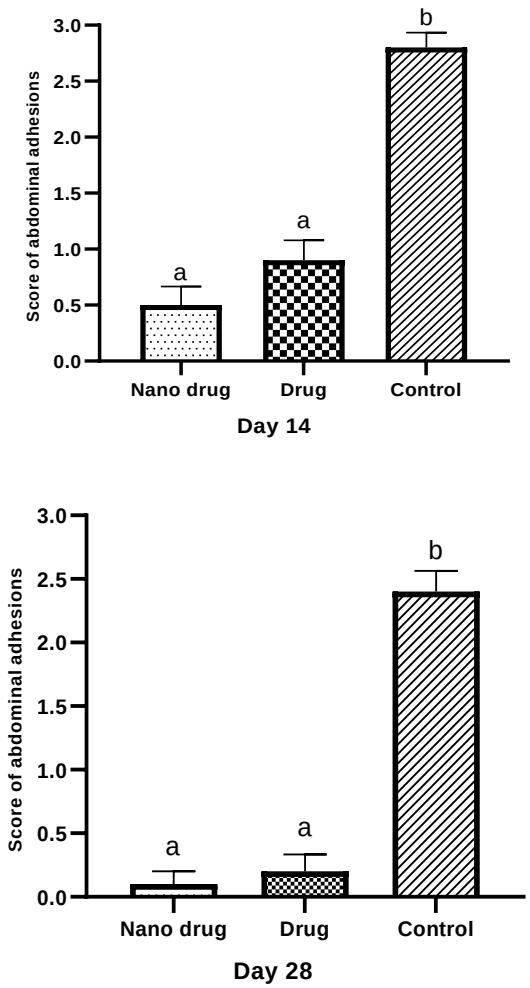

Figure 1. The effect of Nano drug and Drug on macroscopic examination of adhesion in treatment and control groups on days 14 and 28.

Values are given as mean ± SEM (n = 10). Data were analyzed by Kruskal-Wallis and Mann-Whitney U tests. Different letters in each column indicate statistically significant differences ($P < 0.05$).

Microscopic Examination

Histopathological analysis on postoperative day 14 demonstrated significantly reduced inflammatory responses in the nano-tranexamic acid group (50 mg/kg) compared to controls ($P < 0.05$), with the control group exhibiting maximal inflammation. Fibrosis assessment revealed similarly attenuated fibrotic changes in both treatment groups (nano- formulated tranexamic acid and standard tranexamic acid, 50 mg/kg each) versus controls ($P < 0.05$), where the most severe fibrosis was observed (Figures 3 and 4).

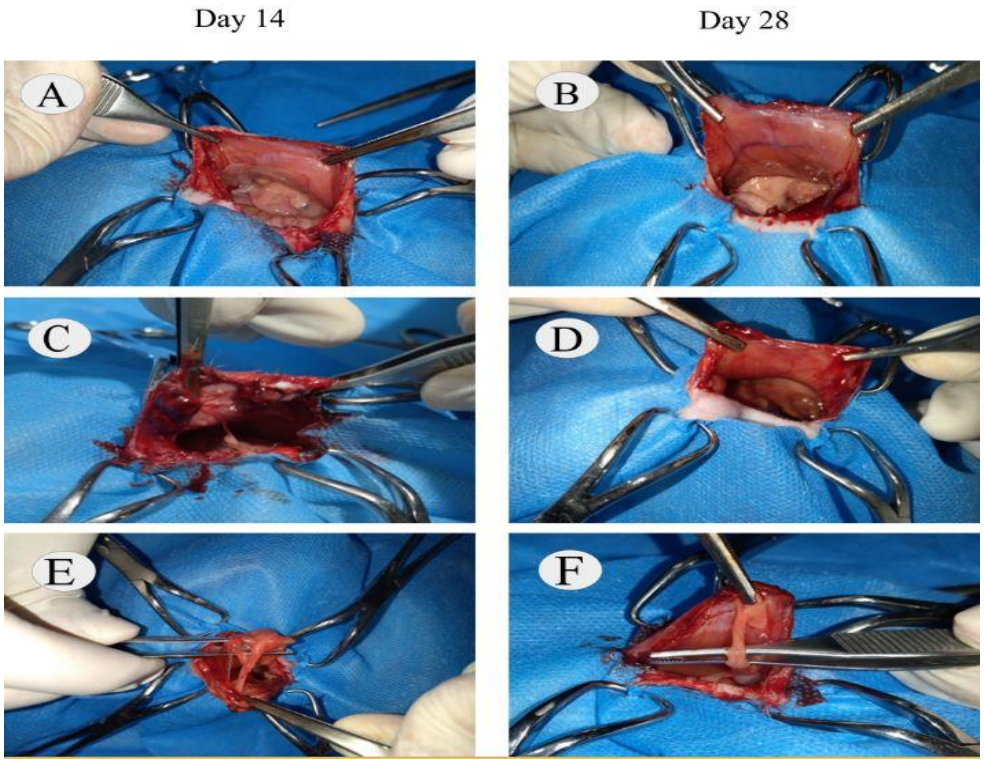

Figure 2. Macroscopic findings of abdominal adhesions. **(A)** Nano-tranexamic acid (50 mg/kg) group on day 14 showing complete absence of adhesions. **(B)** Nano-tranexamic acid (50 mg/kg) group on day 28 demonstrating no adhesion formation. **(C)** Standard tranexamic acid (50 mg/kg) group on day 14 exhibiting minimal adhesions. **(D)** Standard tranexamic acid (50 mg/kg) group on day 28 showing resolution of adhesions. **(E)** Control group on day 14 presenting severe adhesion formation. **(F)** Control group on day 28 maintaining severe adhesions.

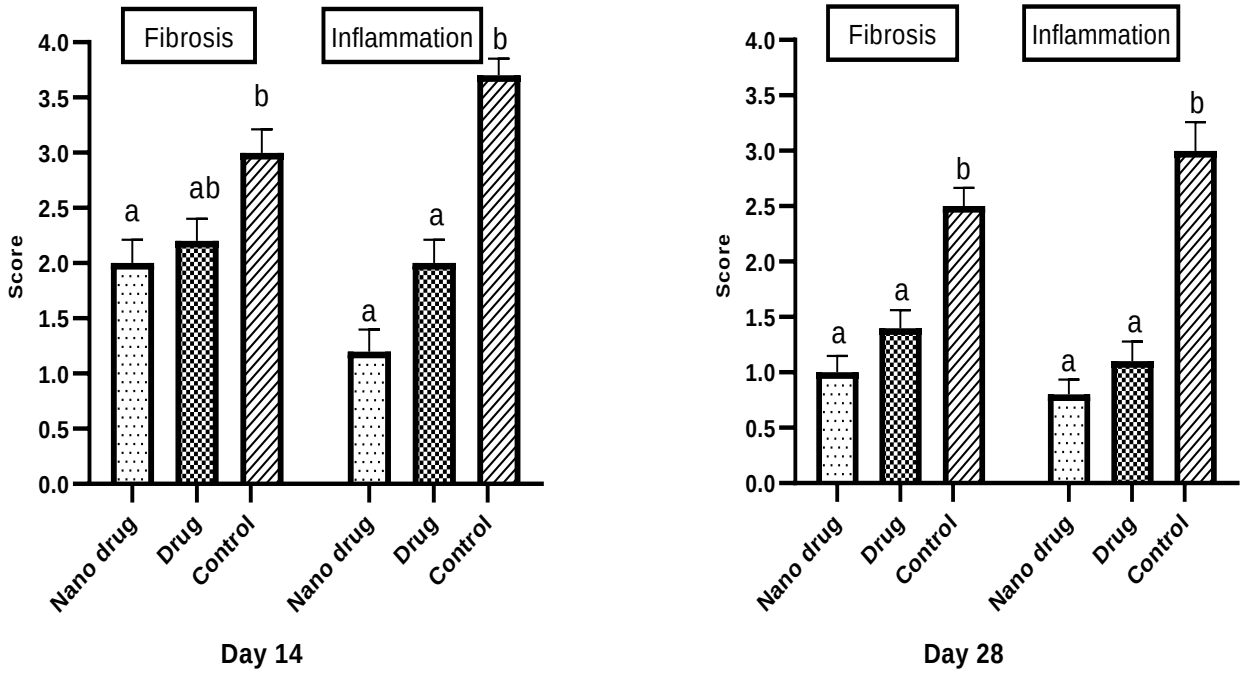

Figure 3: The effect of Nano drug and Drug on macroscopic examination of inflammation and fibrosis index in treatment and control groups on days 14 and 28. Values are given as mean ± SEM (n = 10). Data were analyzed using the Kruskal-Wallis and Mann-Whitney U tests. Different letters in each column indicate statistically significant differences ($P < 0.05$).

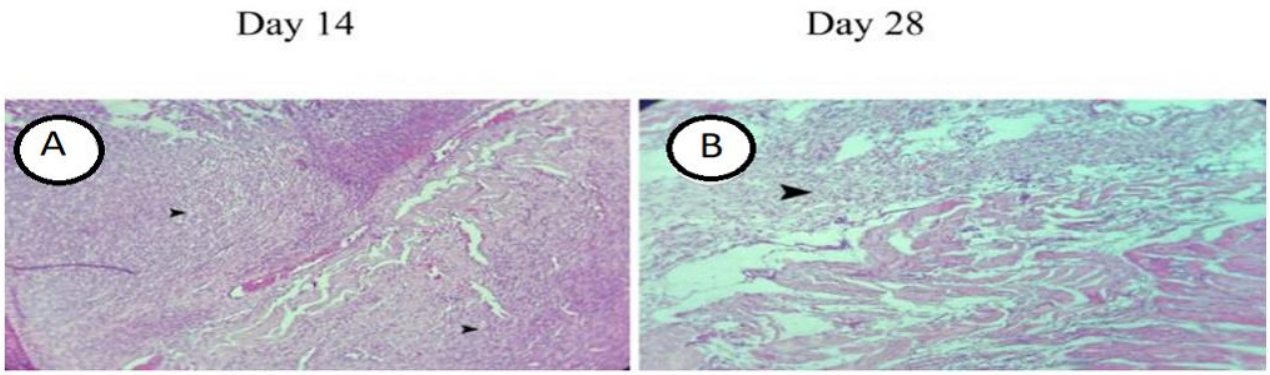

Figure 4: Microscopic sections from the abdominal wall in the Control group. **(A)** On day 14 post-operation, severe infiltration of fibrotic connective tissue (arrowhead) is observed (H&E, 10X). **(B)** On day 28 post-operation, severe infiltration of fibrotic tissue (arrowhead) is seen (H&E, 10X).

Histopathological analysis on day 28 yielded results similar to those on day 14. Notably, the groups treated with the nano-drug and tranexamic acid (50 mg/kg) exhibited the lowest inflammation and fibrosis indices. In contrast, the control group displayed the highest levels of both inflammation and fibrosis. Additionally, a significant difference was observed between the control group and the two treatment groups.

Discussion

The goal of this research was to explore how tranexamic acid nanoparticles influence the reduction of adhesions resulting from laparotomy procedures. The visual assessment of the treatment groups indicated that the group receiving nano-formulated tranexamic acid (50 mg/kg) experienced a marked decrease in adhesions compared to the control group. Furthermore, the histopathological analysis of samples taken from adhesion sites demonstrated significantly reduced inflammatory responses and less fibrotic tissue development in the group treated with nano-drug tranexamic acid (50 mg/kg) relative to the control.

Intra-abdominal adhesions are frequent complications that affect more than half of abdominal surgery patients, leading to various postoperative issues, such as small intestine obstructions, chronic abdominal discomfort, and infertility in women. These adhesions often go undetected and are difficult to identify through standard imaging and laboratory techniques (1, 2).

Research indicates that adhesions occur in 95% of individuals who have undergone laparotomy, resulting from procedures like gastrointestinal surgery, hysterectomy, ectopic pregnancy treatment, and liver and gallbladder surgeries. Over the past decade, numerous strategies have been evaluated to minimize adhesion formation after abdominal operations, including the application of coagulants, fibrinolytic agents, anti-inflammatory medications, antibiotics, and physical barriers (13).

To prevent intra-abdominal adhesions, various strategies have been explored, including suppressing fibroblast proliferation using steroidal compounds, antihistamines, and cytotoxic agents; reducing adhesions with fibrin sealants; and administering diphenhydramine hydrochloride, methylprednisolone, and methylene blue. Additional approaches involve separating intestinal surfaces with pro-peristaltic agents, as well as utilizing heparin, dextran 70, normal saline, antibiotics, promethazine, prostaglandin synthesis inhibitors, Ringer's lactate, and calcium channel blockers. Furthermore, rofecoxib (a cyclooxygenase-2 inhibitor) and octreotide (through inhibition of intraperitoneal myeloperoxidase activity) have demonstrated efficacy in mitigating postoperative peritoneal adhesions. However, these methods, while effective, are associated with undesirable side effects such as coagulation disorders, tissue toxicity, and drug interactions. To address these limitations and enhance therapeutic outcomes, our study introduces an innovative approach using nano-formulated tranexamic acid (TXA). This advanced delivery system leverages targeted antifibrinolytic action and improved biocompatibility to locally inhibit fibrin degradation and modulate inflammatory responses, thereby effectively reducing postoperative adhesions without inducing significant systemic complications.

In a study by Topal et al. (2010), the effectiveness of antifibrinolytic medications in reducing postoperative adhesions was demonstrated. Their research indicated that tissue plasminogen activator (tPA), fondaparinux sodium (FS), and activated drotrecogin alfa (ADA) significantly reduced adhesion formation after laparotomy procedures in rats (14). Our results support the findings

by Topal et al. regarding the role of antifibrinolytic agents in minimizing postoperative adhesions. The decrease in adhesion formation following tranexamic acid treatment is likely due to its capacity to inhibit fibrinolysis and reduce inflammation, facilitating the healing process.

Intraperitoneal bleeding is a well-established risk factor for postoperative adhesion formation. By effectively controlling bleeding and preventing blood accumulation in the abdominal cavity, our results align with existing research demonstrating reduced postsurgical inflammation and adhesion development. This finding corroborates a 2021 meta-analysis by Koh et al., which reviewed 19 randomized controlled trials and found that tranexamic acid (TXA) significantly decreased surgical blood loss and the need for blood transfusions in extrahepatic abdominal procedures without increasing thromboembolic risks (15). Tranexamic acid, a synthetic analog of the amino acid lysine, has properties that inhibit the breakdown of blood clots, making it useful in minimizing blood loss and the need for blood transfusions in surgical patients. This medication can be administered through various methods, including intravenous, intra-articular, oral, topical, or in combination with other treatments (5,6). Research has explored the effectiveness of combining tranexamic acid with substances like gelatin to better control internal bleeding (16).

Additionally, while Smith et al. (2017) showed that administering tranexamic acid can reduce bleeding and the need for blood transfusions, concerns remain about potential risks such as blood clots, stroke, and heart attacks. Nevertheless, studies indicate that patients receiving tranexamic acid during heart surgery may have a lower risk of such complications compared to those who do not (17). Given these risks, local application of tranexamic acid is often considered safer than systemic use.

In our research, we observed that intraperitoneal administration of nano-tranexamic acid (nano-TXA) resulted in a significant reduction in postoperative inflammation, fibrosis, and adhesions in a rat model undergoing laparotomy. These findings align with Wang's 2018 study, which demonstrated that pre- and postoperative intramuscular injections of tranexamic acid (three doses) significantly reduced bleeding, inflammation, and discomfort (5). The use of nano-TXA offers several advantages, including enhanced absorption and targeted delivery to the injury site. The observed reduction in postoperative complications can be attributed to tranexamic acid's well-established antifibrinolytic properties. By inhibiting fibrin degradation, tranexamic acid promotes clot stability, reduces blood loss, and attenuates the inflammatory response.

A 2010 study by David M. Wiseman et al. investigated the efficacy of a fibrin-based product containing tranexamic acid (Adhexil) in preventing adhesions in rabbit uterine horns. Their results showed that Adhexil significantly reduced both the incidence and severity of adhesions in models where the uterine horn adhered to the peritoneal cavity (18). These findings corroborate our research, further supporting the efficacy of tranexamic acid-based compounds in minimizing peritoneal adhesions.

The use of nanotechnology in this study reflects the growing interest in advanced drug delivery systems. Nanoparticles possess unique biological and chemical properties that can improve drug bioavailability, reduce toxicity, and enhance therapeutic efficacy. For adhesion prevention, nanoparticles may improve peritoneal penetration and enable localized TXA delivery to adhesion-prone sites.

The use of nanotechnology in this study reflects the growing interest in advanced drug delivery systems. Nanoparticles possess unique biological and chemical properties that can improve drug bioavailability, reduce toxicity, and enhance therapeutic efficacy. For adhesion prevention, nanoparticles may improve peritoneal penetration and enable localized TXA delivery to adhesion-prone sites.

Our results are consistent with prior studies underscoring TXA's effectiveness in reducing intra-abdominal adhesions. A 2004 study by David M. Wiseman et al. involving 228 male rats found that incorporating TXA into a fibrin sealant significantly decreased adhesion incidence and severity post-laparotomy (19). We observed similar outcomes in our study, particularly in the nano-TXA group during the 28-day follow-up period.

Conclusion

In conclusion, the intraperitoneal administration of nano-tranexamic acid (50 mg/kg) significantly reduces intra-abdominal adhesions after laparotomy. Additionally, it mitigates inflammatory responses and fibrotic tissue formation at adhesion sites.

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Not applicable.

Authors' Contributions

Salar Zehforoush: Conceptualization, Formal analysis, Investigation, Methodology. **Alireza Jahandideh:**

Conceptualization, Supervision, Investigation, Methodology, **Mohammad Mahdi Alinaghizadeh:** Writing original draft, Review and editing, **Hamed Karimi,** Investigation, Methodology.

Data Availability

All data are included in this published article.

Ethical Approval

All applicable international, national, and institutional guidelines for the care and use of animals were followed.

Conflict of Interest

The authors affirm that there are no competing interests or potential conflicts of interest associated with the publication of this work.

Consent for Publication

Not applicable.

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