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EVALUATION OF THE ANTI-ADHESIVE EFFICACY OF GELATIN SPONGE AND ALGINATE SPONGE IN THE PREVENTION OF POST-SURGICAL INTRA-ABDOMINAL ADHESIONS

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ABSTRACT

The occurrence of intra-abdominal adhesions after abdominal surgical interventions is considered an important issue in veterinary clinics. Although several adhesion-reducing agents were evoked to overcome the formation of such intra-abdominal adhesions, their effectiveness was still unsatisfactory. Hence, the present study assessed and compared the antiadhesive capability of gelatine and alginate sponges to minimize or prevent the formation of post-surgical intra-abdominal adhesions in a rabbit model. The cecal abrasion model was induced in animals and left untreated as control positive or treated with either intra-abdominal application of gelatine sponge (GS) or alginate sponge (AS). Clinical observation, gross appearance and histological evaluations were performed after 2 weeks of surgery. Grossly, the gelatine sponge enhanced the formation of intra-abdominal adhesions compared to the alginate sponge and control positive groups. Furthermore, both GS-treated and sham groups revealed no fibrosis on histological outcomes. The AS-treated group induced an extensive reaction with the formation of a marked degree of fibrosis and inflammatory cell infiltration. It was concluded that a gelatine sponge possesses the potential to prevent adhesions that could be formed intra-abdominally after abdominal surgery. An alginate sponge stimulates the formation of these adhesions.

Keywords: intra-abdominal; adhesions; gelatine; alginate; anti-adhesion.

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INTRODUCTION

The development of intra-abdominal adhesions is an eventual consequence of abdominal surgical interference in human and veterinary practice. These post-operative abdominal adhesions, developed in more than 90% of patients after intra-abdominal surgery, may result in significant morbidity and mortality with financial burden. In addition, these abdominal adhesions can lead to complications such as pain, infertility, bowel occlusion, and even death (Alonso *et al.*, 2014; Yu *et al.*, 2014; Ibrahim *et al.*, 2022). The strategy for the treatment of such post-surgical peritoneal adhesions depends on the re-operation to get rid of these adhesions; however, these adhesions can obliterate the surgical approach and the surgical field visibility during the additional surgical interventions that are also associated with the risk of second surgery (Gorvy *et al.*, 2008; Ibrahim *et al.*, 2022).

The usage of adhesion-reducing substances is considered an alternative to avoid intra-abdominal adhesions after abdominal surgery. A diverse of materials have been reported with varying effectiveness in the prevention or reduction of these intra-abdominal adhesions including starch, sodium bicarbonate (Hamid & Ramezani, 2004), honey (AA, 2006), collagenase (Cakir *et al.*, 2013), heparin (Sharifi *et al.*, 2007), lidocaine HCl (Mariano *et al.*, 2015), vitamin E and selenium (Durmus *et al.*, 2011), cephalosporins (Kayaoglu *et al.*, 2013), chitosan (Wei *et al.*, 2009), gelatine (Ibrahim *et al.*, 2022), and dexamethasone (Zomorrodi *et al.*, 2011). However, the most effective one for the complete prevention of the formation of such adhesion is still missing (Lih *et al.*, 2015; Fatehi Hassanabad *et al.*, 2021).

Among different substances, gelatin is regarded as an anti-inflammatory protein, extracted via the thermal denaturation of collagen (Zhu *et al.*, 2018). Gelatin is a biocompatible, non-toxic, nonallergenic, absorbable material that elicits no immunological response (Hajosch *et al.*, 2010; Ibrahim *et al.*, 2022). It has an important role in anti-cancer medication delivery, wound dressings, food safety, bone regeneration, and tissue engineering as nanomedicine advances (El-Seedi *et al.*, 2023; Ju *et al.*, 2023; Tan *et al.*, 2023; Cao *et al.*, 2024). In addition, gelatine sponges were reported to be beneficial for hemostasis during surgical operations, in which traditional hemostasis is difficult or impractical and other non-absorbable materials are unsuitable (Hajosch *et al.*, 2010). Furthermore, gelatine sponges minimize the incidence of postoperative intra-abdominal adhesions (Ibrahim *et al.*, 2022).

Alginate is another material that naturally occurring anionic polymer typically obtained from brown seaweed and has been extensively investigated and used for many biomedical applications, due to its biocompatibility, low toxicity, relatively low cost, and mild gelation by addition of divalent cations such as Ca^{2+} (Lee & Mooney, 2012). Alginate sponge is a biodegradable and biocompatible material that is used for hemostasis, post-surgical tissue adhesion barrier, and wound dressing (Cho *et al.*, 2010; Mndlovu *et al.*, 2019; Lv *et al.*, 2022).

The objective of this study is to investigate the anti-adhesive efficacy of gelatin sponge and alginate sponge in the prevention of post-surgical intra-abdominal adhesions in a rabbit cecal abrasion model. In addition, it aims to compare the potential of a gelatin sponge to an alginate sponge in decreasing the rate of intra-abdominal adhesion occurrence following surgery.

MATERIALS AND METHODS

Ethical approval

The study was approved by Assiut Veterinary Medicine Research Ethics Committee No. 06/2024/0205 by the Egyptian bylaws and OIE animal welfare standards for animal care and use in research and education.

Experimental animals and design

The experimental study was conducted on 20 healthy 4-month-old New Zealand white female rabbits weighing 2.5-3.0 kg (mean=2.68kg). The maintenance and health monitoring of the experimental rabbits were done according to the international recommendations (Mähler *et al.*, 2014). Rabbits were housed individually in cages in a well-ventilated room at the Veterinary Teaching Hospital, Faculty of Veterinary Medicine, Assuit University, and were fed on a diet of standard commercial rabbit chow and access to water was *ad libitum*.

The animals were equally and randomly divided into 4 groups (n=5 in each group), according to the used anti-adhesive material. Rabbits treated with gelatin sponge (GS group), rabbits treated with alginate sponge (AS group), or were left untreated in control positive (CP group) and sham (SH group) groups. *In vivo*, the performance of the materials was evaluated at 2 weeks after induction of the cecal abrasion model along with control groups.

Establishment of cecal abrasion model and management

The animals were thoroughly evaluated to ensure that they were all healthy. The rabbits were acclimatized to their new living unit for 14 days before the surgical procedures began. All animals were starved for 8 hours before surgery and given free access to water.

General anesthesia was induced and maintained using isoflurane (Forane ®: AbbVie, England) in 100% oxygen by masking and a non-rebreathing system. Anesthesia was induced with isoflurane (5%) in oxygen (2 L/minute), anesthesia was established within 1-3 minutes indicated by loss of both ear pinch and jaw tone reflexes. Anesthesia was maintained with isoflurane (2.5-3%) in oxygen (2 L/ minute) (Sadek *et al.*, 2023)**.** The animals were monitored for changes in vital signs including breathing and heart rate during surgery as well as the response to pain to control the level of anesthesia. Moreover, eye reflexes and the color of mucous membranes were observed.

All surgical procedures were performed under strict aseptic conditions. The anesthetized rabbit was positioned in dorsal recumbency. The ventral abdominal wall was prepared for aseptic surgery through shaving, scrubbing with Povidone Iodine 10% (Betadine ©, El Nile Co. for Pharmaceutical and Chemical Industries, Cairo, Egypt), and finally draping of the operation site.

The experimental cecal abrasion model was induced according to Dhall *et al.* (2019) as illustrated in Figure 1. In brief, an umbilical midline celiotomy was performed through a 4-cm midline abdominal cutaneous and muscular incision using a scalpel blade size 15 for each animal. The cecum was exteriorized and scratched on the surface opposite to the incision line through scrubbing for 15 min with a sterile toothbrush until petechial hemorrhage was seen. The abraded cecum was then returned to its normal position in the abdominal cavity. Then rabbits were randomly divided into four groups as follows; Intra-abdominal application of gelatine sponge (GELITA-SPON®: Gelita Medical, Germany) in GS group (*n*=5), or alginate sponge (Kaltostate®: ConvaTec, United Kingdom) in AS group (*n*=5). However, the positive control group (PC group, *n*=5) was left untreated, whereas in the sham group (SH group, n=5), the cecum was left without induction of abrasion. Finally, in all rabbits, the abdominal wall was sutured using polyglactin 910 (Vicryl, USP 3-0, M-NATUR®, International Sutures Manufacturing Co., Egypt) in a simple continuous manner followed by closure of the skin using silk (Silk USP 3-0, M-NATUR®, International Sutures Manufacturing Co., Egypt) in a simple interrupted suture.

Animals were then transferred into their cages and monitored until complete post-operative recovery and then for 14 days, post-surgery, for any abnormal clinical signs. Animals were allowed to move inside their cages without restriction and given their traditional regimen of food and water after the operation. The wound and the physiological condition of the rabbits were under close observation. At the end of the study (2 weeks after implantation), rabbits were sacrificed, and the abdominal cavities were incised carefully and examined grossly. Samples were harvested for histopathologic evaluation of intra-abdominal adhesion.

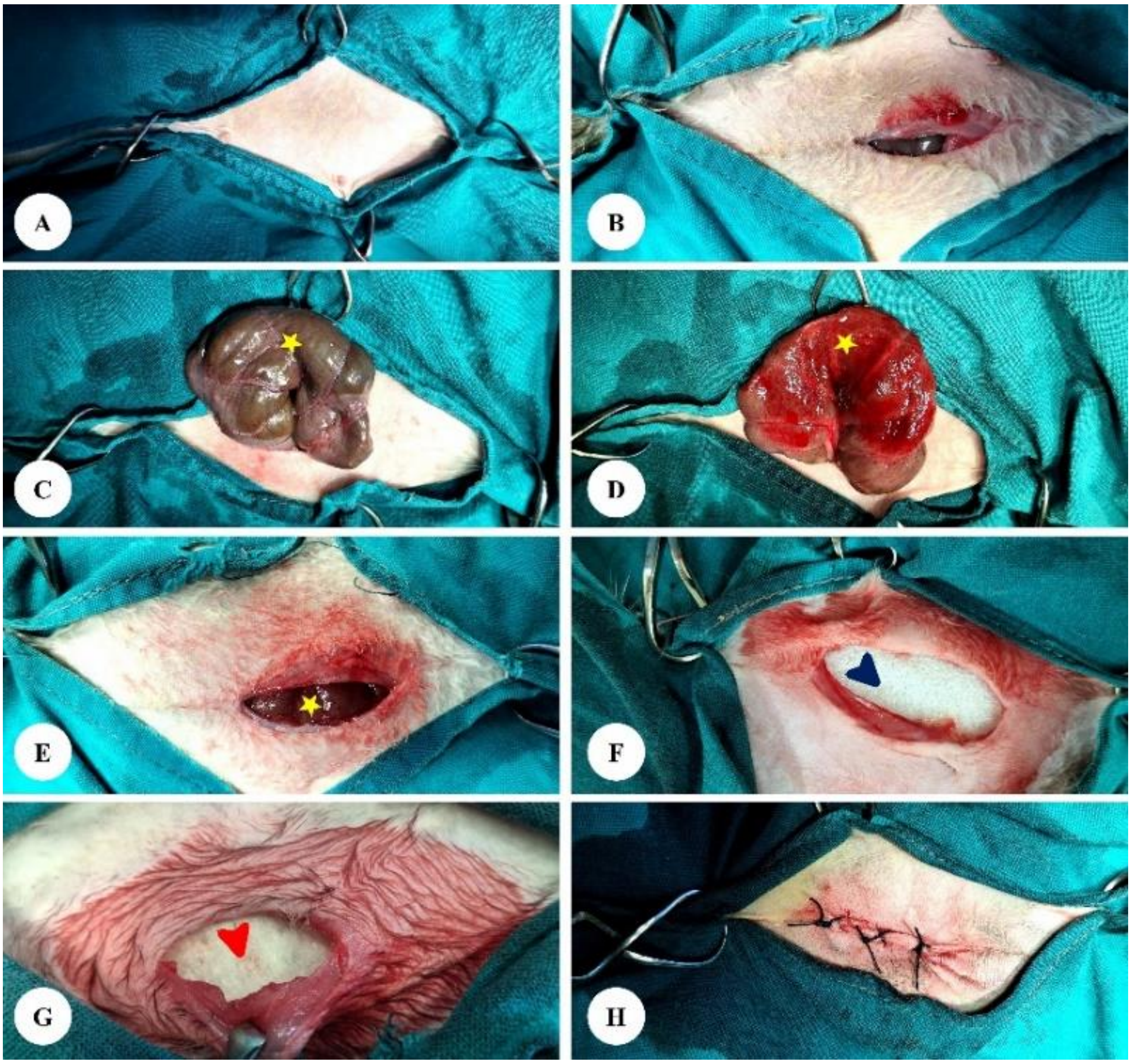

Fig. 1: Surgical procedure of cecal abrasion induction and application of sponges. Aseptic preparation **(A)**, ventral abdominal wall incision **(B)**, exteriorization of the cecum (yellow asterisk) **(C)**, abrasion of the cecum (yellow asterisk) **(D)**, returning the abraded cecum to the normal abdominal position **(E)**, application of gelatine sponge (blue arrowhead) **(F)**, application of alginate sponge (red arrowhead) **(G)**, and abdominal wall closure **(H)**.

Clinical observation

All animals were subjected to daily clinical examination of any surgical complications, which included evidence of infection which was assessed via rectal temperature, appetite, and wound dressing. Additionally, any signs of illness and general reaction to surgery and treatment were recorded.

Gross examination

After sacrification, the entire abdomen was opened through a midline celiotomy incision from the xiphoid cartilage to the *os pubis*. Abdominal contents were thoroughly inspected for the presence of adhesions. A score system for intra-abdominal adhesions was developed to numerically record the degree of adhesions according to (Ibrahim *et al.,* 2022) as follows; No adhesion (*score 0*), one adhesive band either between the organs or between the organs and abdominal wall (*score 1*), two adhesive bands either between the organs or between the organs and abdominal wall (*score 2*), more than two adhesive bands between the organs or between the organs and abdominal wall or adhesions of the whole intestinal tract without the abdominal wall (*score 3*), and adhesion of the viscera directly to the abdominal wall (*score 4*).

Histopathological analysis

Samples from the skin of the abdominal wall and cecum at the site of adhesion from each group were harvested and fixed in 10% neutral buffered formaldehyde (pH 7.2) for more than 3 days. Then, dehydrated through a gradient ethanol series (70–100%), and cleared in xylene, before embedding in paraffin wax, and 5-μm sections were prepared using a microtome. The sections were deparaffinized, rehydrated, and washed in distilled water (Ibrahim *et al.*, 2022).

The slides underwent histological evaluation using hematoxylin and eosin (H&E) stain and histochemical evaluation using Masson's trichrome staining (MT). Stained sections were examined under light microscopy (Olympus CX31, Japan) and photographed using a digital camera (Olympus, Camedia C-5060, Japan). Histological examination was carried out depending on the extent of cellular inflammation, and fibrous tissue formation to further assess the anti-adhesive efficacy of gelatin sponge and alginate sponge in preventing post-surgical intra-abdominal adhesions by using H&E staining and use MT staining for identifying collagen fibers deposition.

Statistical analysis

Data were presented as mean ± standard deviation (SD). The results of adhesion scores (n=5 for each group) were analyzed by one-way ANOVA, followed by Tukey's test. The significance level was set at $P < 0.05$. Statistical analysis was performed with IBM® SPSS® Statistics Version 21 for Windows.

RESULTS

Clinical investigation

In the present study, the rabbits in all groups recovered smoothly from the anesthesia, which was enough for performing the surgical operations. Rabbits started eating their food and drinking water shortly after recovery from anesthesia. Furthermore, no signs of illness and general reactions to surgery were noticed throughout the experiment. Skin wounds completely healed by primary intention healing without complications. No swelling or oedema was recorded at the skin wound.

Gross evaluation

All rabbits in the CP group showed a severe degree of intra-abdominal adhesions of grades 3 and 4 (Fig.2Aa). These thick bands of adhesions were seen to form between the abdominal wall and the cecal serosa. However, animals of the SH group displayed an absence of intra-abdominal adhesion formation throughout the entire abdomen (Fig.2Ab).

The examination of the GS group demonstrated the absence of any intra-abdominal adhesion bands (Fig.2Ac) except one rabbit showed grade 2 adhesions (Fig.2Ad). In addition, the gelatine sponges were absent throughout the whole abdominal cavity, indicating complete absorption of the gelatine sponges.

In the AS group, gross examination showed an extensive formation of intra-abdominal adhesions of degree 4 between the cecum and abdominal wall (Fig.2Ae, f). The alginate sponges were still observed with the presence of a suppurative reaction surrounding the sponge. Furthermore, severe adhesion bands were recorded between the alginate sponge, cecal serosa, and loops of the small intestine. Regarding the score of adhesion grossly (Fig.2B), the rabbits in the GS group showed a significantly decreased mean adhesion score (0.40 ± 0.89) compared to those of both CP and AS groups (3.40± 0.54 and 4.00 ± 0.00, respectively).

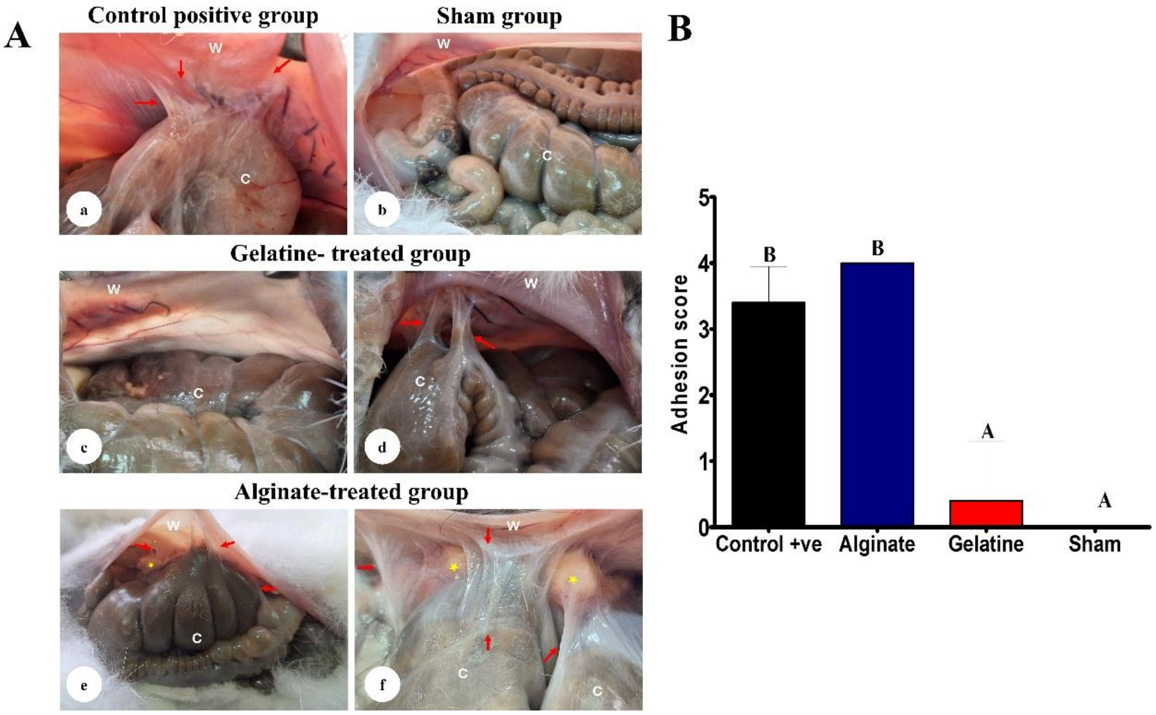

Fig. 2. Gross evaluation of intra-abdominal adhesions. **(A)** Gross appearance of rabbit abdomen of control positive (a), sham (b), GS-treated (c, d), and AS-treated (e, f). **(B)** A graph showing the intra-abdominal adhesion score of the different groups at 2 weeks after surgical operations. Error bars ± SD; n = 5 for each group Bars with the same letter represent values that are not significantly different. A and B Mean ± S.D. with different letters are significantly different at $P < 0.05$. *W* abdominal wall, *C* cecum, red arrows: adhesion bands; yellow asterisk: alginate sponge.

Histological assessment

The CP group revealed infiltration of inflammatory cells at the adhesion site. In addition, the adhesion site exhibits deposition of large amount of fibrous tissue between the cecal serosa, peritoneum, and abdominal skeletal muscle (Fig.3A, B). Whereas the SH group slides showed no intestinal adhesions, no inflammatory cells, and normal intestinal architecture (Fig.3 C, D).

In the GS group, mild inflammatory cell reactions without evidence for adhesion between intestinal and abdominal walls were observed (Fig.3 E, F). However, the AS group showed intestinal-peritoneal adhesion with a thickened layer of inflammatory reaction consisting of alginate, connective tissue and inflammatory cells (Fig.3 G, H). Hyperemic blood vessels and neovascularization were noted. The AS group reported significant infiltration of inflammatory cells in the adhesion tissues, including giant cells, lymphocytes, and plasma cells.

Regarding the decalcified paraffin sections stained with MT, CP sections demonstrated deposition of thick and dense layer of collagen fibres with the presence of fibroblasts (Fig.4A) compared to non-detectable collagen fibers deposition in both SH (Fig.4B) and GS (Fig.4C) groups. However, the AS group displayed a thick and dense layer of deposited collagen fibers associated with fibroblast cells (Fig.4D).

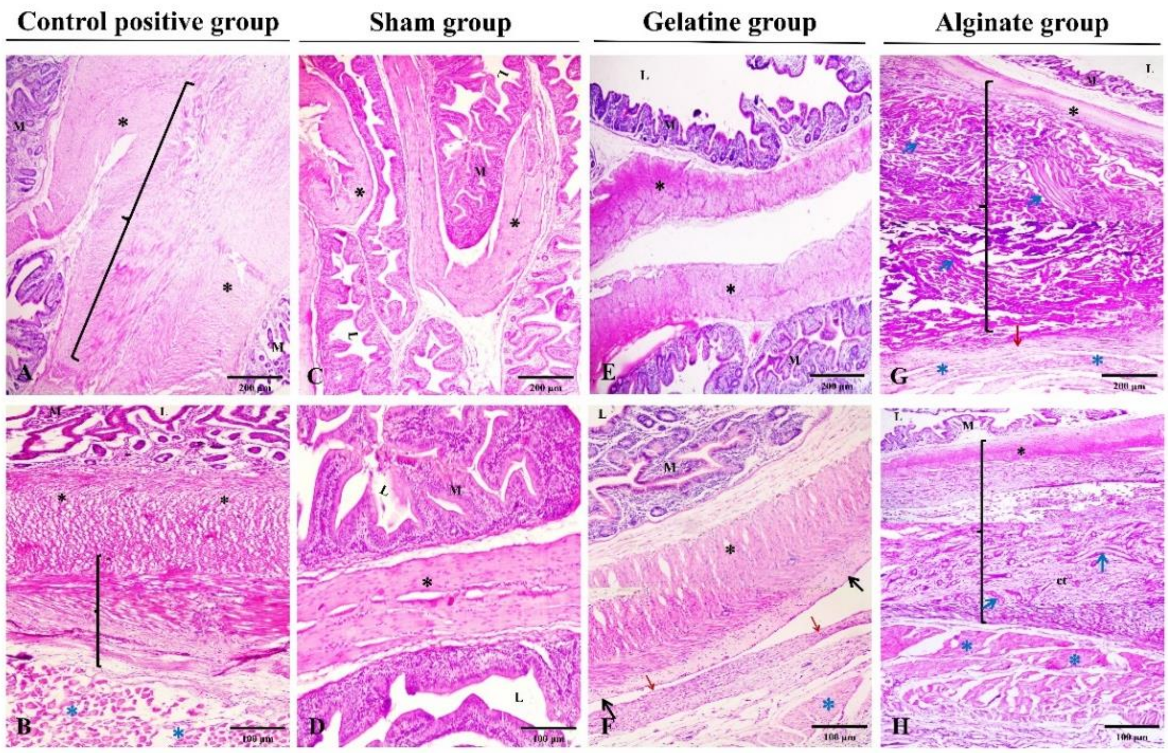

Fig. 3. Histological evaluation of intra-abdominal adhesion formation. The adhesion tissues were stained with hematoxylin and eosin from the control positive (A, B), sham (C, D), GS-treated (E, F), and AS-treated (G, H) groups. The scale bars in panels A, C, E, and G= 200 µm, and panels B, D, f, and H = 100 µm (×100). L: intestinal lumen; M: mucosa; black asterisks: muscular layer; blue asterisk: skeletal muscle; black bracket: adhesion site; red arrows: peritoneum; black arrows: abdominal wall skeletal muscles; blue arrows: alginate.

DISCUSSION

Cecal abrasions with consequent adhesions were induced successfully in rabbits of the present study. Gelatine, however, prevented these adhesions in contrast to alginate which failed to prevent or minimize them.

In the present study, the PC group showed a severe degree of abdominal adhesions with extensive fibrous tissue deposition and inflammatory cell infiltration, suggesting that a successful model of cecal abrasions in rabbits as reported previously (Yu *et al.*, 2014; Dhall *et al.*, 2019; Ibrahim *et al.*, 2022). The intra-abdominal adhesions formation between the surfaces of abdominal tissues and each other or the peritoneum represents a challengeable health problem with serious complications including abdominal pain, evidence of intestinal blockage, dietary intolerance, female infertility, and requirement for a relaparotomy (Ellis *et al.*, 1999; Fukuhira *et al.*, 2008; Basbug *et al.*, 2011; Junga *et al.*, 2019; Güler *et al.*, 2023). These adhesions mainly developed after abdominal surgical operations due to injury of the peritoneal surface and serosal surfaces or tissue ischemia caused by traumatic manipulation of the organs during surgery contributing to the initiation of peritoneal inflammation and the formation of scar tissue extensively.

Furthermore, the presence of infection plays a role in the formation of abdominal (Reijnen *et al.*, 2003; Arung *et al.*, 2011; Güler *et al.*, 2023). It has been cited that after abdominal surgery, the development of peritonitis resulted in an imbalance between the rate of fibrin breakdown and deposition promoting the formation of the fibrinous exudate, which either resorbed by the body or deposited and rearranged

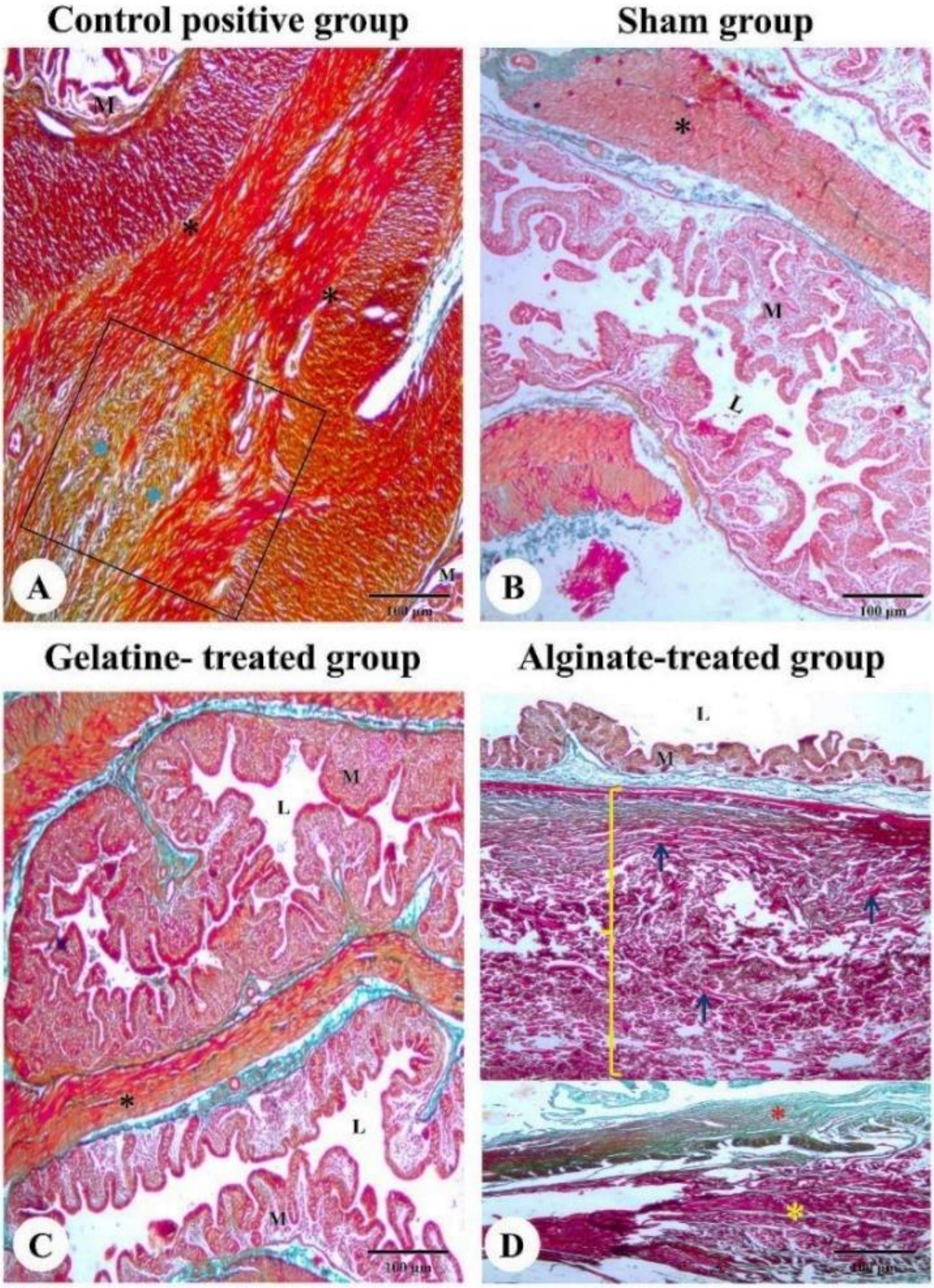

Fig. 4. Histological evaluation of intra-abdominal adhesion formation. The adhesion tissues were stained with Masson's trichrome from the control positive (A), sham (B), GS-treated (C), and AS-treated (D) groups. The scale bars in panels A-D = 100 µm. L: intestinal lumen; M: mucosa; black asterisks: muscular layer; blue asterisk: fibrous tissue; red asterisk: peritoneum; yellow asterisk: skeletal muscle; black arrows: alginate.

following fibroblasts migration, forming undesirable persistent fibrosis (Arung *et al.*, 2011; Ward & Panitch, 2011; Ibrahim *et al.*, 2022). However, in a normal abdomen, the fibrinous adhesions were broken down through the action of naturally existing enzymes of fibrinolysis. In contrast, in the injured abdomen, the activity and production of such fibrinolytic enzymes were diminished causing the persistence of fibrinous adhesions. These fibrinous adhesions were invaded by the tissue repair cells as macrophages, fibroblasts, and blood vessel cells to deposit collagen fibers and extracellular matrixes that finally develop intra-abdominal fibrous adhesions (Ibrahim *et al.*, 2022).

Herein, the intra-abdominal application of gelatine sponge in rabbits of the GS group revealed a desirable outcome in minimizing the formation of abdominal adhesions compared to the CP group. These results indicated the ability of the gelatine sponge to be used as an anti-adhesive material for the prevention of post-surgical abdominal adhesion formation (Ibrahim *et al.*, 2022). It is suggested that the antiadhesive effect of gelatine sponges might be accompanied by the reduction of inflammation and macrophage activity due to the anti-inflammatory properties of gelatine sponges (Zhu *et al.*, 2018). In addition, it is reported that gelatine sponges decrease the proliferation and activity of fibroblast cells, inhibiting the deposition of fibrin and collagen fibers on the site of injury, and encouraging fibrinolysis (Miyamoto *et al.*, 2006; Ibrahim *et al.*, 2022). Furthermore, gelatine sponge acts as a physical barrier interposed between the injured serosa and peritoneum as well as controls the hemorrhage phase of inflammation, a crucial to avoid intra-abdominal adhesion, via the hemostatic activity (Brochhausen *et al.*, 2011; Torii *et al.*, 2017; Ibrahim *et al.*, 2022). Our results agreed with previous studies that reported the efficiency of various gelatine-based composites in the prevention of abdominal adhesions following surgery (Miyamoto *et al.*, 2006; Hajosch *et al.*, 2010; Bae *et al.*, 2014; Hu *et al.*, 2015; Tian *et al.*, 2015; Torii *et al.*, 2017; Ibrahim *et al.*, 2022).

It is worth mentioning that the application of alginate sponge in this work demonstrated the formation of massive intraabdominal adhesions between the cecum and abdominal wall and organs associated with extensive recruitment of inflammatory cells and formation of fibrous adhesions, indicating that alginate sponge is regarded as unsuitable material for the reduction nor prevention of intraabdominal adhesions after surgery. This could be attributed to the presence of calcium ions (Ca^{+2}) as a constituent of the alginate sponge. It was reported that the Ca^{+2}, a crosslinking agent for alginate, release from the calcium alginate *in vitro* and *in vivo* is associated with stimulation inflammatory reaction via induction of production of various inflammatory cytokines (Chan & Mooney, 2013). Additionally, It has been proposed that alginate material initiated the recruitment of neutrophils, macrophages, and monocytes via the Nuclear factor-kappa B (NF-κβ) pathway, resulting in the production of proinflammatory mediators including interleukin-6 (IL-6), IL-12, IL-1β, and tumor necrosis factor- α) (TNF- α) (Yang & Jones, 2009; Chan & Mooney, 2013; Paredes Juárez *et al.*, 2014; Hernández-González *et al.*, 2020; Elalouf, 2021). Furthermore, numerous investigations have documented the identification of antibodies against alginate *in vivo* (Johansen *et al.*, 1991; Kulseng *et al.*, 1999; Chan & Mooney, 2013).

In the present study, the main limitations include the use of a small sample size and insufficient proof of the results on the level of proteins using immunohistochemistry analysis or on gene level using PCR. Future studies should be focused on *in vitro* experiments as well as the degradation of the materials. In addition, further studies should be carried out on another adhesion model to assess the antiadhesive ability of the materials.

CONCLUSION

In conclusion, the findings in the present experimental study revealed the success of the intra-abdominal application of gelatine sponge in the reduction of the rate of occurrence of post-surgical abdominal adhesions. Moreover, gelatine sponge application is regarded as economical, safe, and easily applied. On the contrary, the use of alginate sponge is detrimental and regarded as a causative agent for induction of extensive formation of intra-abdominal adhesions. Finally, the current study suggests the intra-abdominal application of a gelatine sponge following abdominal surgery to prevent the incidence of intra-abdominal adhesion formation.

Abbreviations

AS: Alginate sponge, Ca^{+2}: Calcium ions, GA: gelatine sponge, H&E: hematoxylin and eosin, IL: interleukin, MT: Masson's trichrome, NF-κβ: Nuclear factor-kappab, TNF-α: tumor necrosis factor-alpha.

Conflict of interest

The authors declare no competing interests.

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Author contributions

A. A. S.: Conceptualization, Methodology, Investigation, Data curation, and Writing – review & editing, Formal analysis, Validation, and Supervision. **H.E.:** Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing, and Formal analysis. **K.R.:** Methodology, Investigation, Data curation, and Writing – review & editing, Formal analysis, Validation, and Supervision. **A.F.A.:** Conceptualization, Methodology, Investigation, Data curation, and Writing – review & editing, Formal analysis, Validation, and Supervision. All authors reviewed the manuscript and approved the final version for publication.

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تقييم الفاعلية المضادة للالتصاقات لإسفنج الجيلاتين وإسفنج الألجينات فى منع حدوث الالتصاقات داخل البطن بعد الجراحة

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يعتبر حدوث التصاقات داخل البطن بعد التدخلات الجراحية في البطن مشكلة مهمة في الحقل البيطري. على الرغم من استخدام العديد من المواد لتقليل الالتصاق والتغلب على تكوين مثل هذه الالتصاقات داخل البطن، إلا أن فعاليتها لا تزال غير مرضية. ومن ثم، قامت الدراسة الحالية بتقييم ومقارنة القدرة المضادة للالتصاق لكلاً من إسفنجات الجيلاتين و الألجينات لتقليل أو منع تكوين التصاقات داخل البطن بعد الجراحة في نموذج الأرنب. تم إحداث نموذج كشط الأعور في الحيوانات وترك دون علاج كمجموعة ضابطة ايجابية أو تمت معالجته إما باستخدام إسفنجة الجيلاتين أو إسفنجة الألجينات داخل البطن. تم إجراء المراقبة السريرية والفحص الظاهري للبطن والتقييمات النسيجية بعد أسبوعين من الجراحة. أظهرت إسفنجة الجيلاتين تحسنًا إيجابيًا في منع تكوين الالتصاقات داخل البطن مقارنةً بإسفنجة الألجينات والمجموعات الضابطة الايجابية. وعلاوة على ذلك، كشفت كلا من مجموعة إسفنجات الجيلاتين والمجموعة الضابطة السلبية عن عدم وجود علامات لحدوث الالتصاقات في النتائج النسيجية. بينما تسببت المجموعة المعالجة بـ الألجينات في حدوث تفاعل واسع النطاق مع تكوين درجة ملحوظة من التليف ووجود الخلايا الالتهابية في الفحص النسيجي. يمكن الاستنتاج من نتائج هذه الدراسة أن إسفنجة الجيلاتين تمتلك القدرة على منع الالتصاقات التي يمكن أن تتشكل داخل البطن بعد جراحة البطن، في حين أن إسفنجة الألجينات تحفز تكوين هذه الالتصاقات.