Role of Chitosan Application in Postoperative Abdominal Adhesions in Rabbits

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Summary

This study was performed to evaluate the reliability and efficacy of intra-peritoneal performances of chitosan powder in preventing abdominal adhesions following laparotomy. Twenty clinically healthy rabbits of both sexes, weighing 1.5-2 kg were allocated randomly into 2 equal groups; control group (G1) and treated group (G2). After surgical preparation the animals had undergone to laparotomy which was performed to create a sero-muscular incision of 4cm length in the stomach, in G1 the incision was closed by suturing stomach wound and abdominal wall, While (G2) animals were subjected to same operation but after stomach incision suturing, 1gr. of chitosan powder was sprinkled on stomach incision and peritoneal cavity prior to the lina alba and skin closures. 5 animals of each group were euthanized at two periods: 7^{th} and 21^{st} day post operation, adhesions in abdominal cavity were examined macroscopically and microscopically. The results showed clearly no adhesions at the operation site (the stomach wound), also on all abdominal organs and peritoneum cavity in both examination periods in G2. In conclusion this study revealed that chitosan plays a vital role in restrictions of intra-abdominal adhesion even though the mechanism of action is still unknown.

Keywords: Intra-peritoneal, Adhesion, Chitosan, Laparotomy.

Introduction

Adhesions are major complications of healing and inescapable consequence following surgery or infection which can lead to conditions such as intestinal obstruction, sterility, and protracted pain (1). Post-surgical adhesion arises when fibrous threads of scar tissue form, leading to abnormal union of anatomical structures of the abdomen (2) that occurs when a natural defending barrier avoids the organs from adhering to nearby apposing surfaces carried by the mesothelial cells of the peritoneum, reduced or vanished during inflammatory or hurtful processes that affect integrity and continuity of the serosa (3). Several drugs and substances are used locally or systematically for preventing this condition, Although specialists have used numerous means to decrease adhesion development at each step of adhesion formation, honey (4) Methylene Blue (5) and long list of materials comprises corticosteroids, antihistamine, dextran, saline, aprotinin, octreotide and heparin, no idyllic method has been found for this purpose, while Intra-abdominal administration of some anti-adhesive barriers, such as a bioresorbable membrane consisting of sodium hyaluronate and carboxymethyl-cellulose (Seprafilmtm), may reduce postoperative adhesions, as demonstrated by some animal models and clinical studies. (6 and 7) Chitosan is a natural polymer (poly D glucosamine) obtained by deacetylation of chitin so it is known as Deacetychitin. Chitin is the second most abundant polysaccharides in nature after cellulose. The main commercial source of chitin is the shell waster of shrimp, crab, lobster, krill, and squid. It's biologically safe, non-toxic, biocompatible and biodegrade-able polysaccharide. Act as a bioadhesive polymer and having antibacterial activity, chitosan is a good candidate for site-specific drug delivery (8), it exhibits myriad of biological actions, namely hypercholesterole-mia, antimicrobial and wound healing properties, low toxicity coupled with wide applicability makes it a promising candidate not only for the purpose of drug delivery for a host of drug moieties, (anti-inflammatory, peptides, etc), but also as a biologically active agent (9). Aim of study to evaluate the reliability and efficacy of intra-peritoneal performances of chitosan powder in preventing abdominal adhesions following laparotomy.

Materials and Methods

The Ethics Committee of our faculty approved the experimental procedures in this study. All of the guiding principles in the care and use of laboratory animals were strictly adhered to throughout the entire study. Twenty clinically healthy local breed rabbits of both sexes, weighing 1.5-2 kg were used in the present study, they were allocated randomly into two groups, control (G1) and treated group (G2). All animals have been fasted for 12 hours before operation. The operation site was prepared surgically. Xylazine 5mg\ kg B.W. was used as premedication. Followed after five minute by IM injection of mixture of midazolam 3mg/ kg. BW with ketamine hydrochloride 40mg\ kg (10). Animals were placed in a dorsal recumbence, underwent to median laparotomy, then stomach was pulled out the abdominal cavity and visceral gastric surface was hold with two stay sutures, then surgical incision between greater and lesser curvature of stomach was performed about 4 cm in length without including the mucosa, this wound was closed with 3.0 USP chromic catgut simple continues pattern, followed by closure of linea alba by same pattern with 2.0 USP chromic catgut, finally the skin was closed 2.0 silk by simple interrupted that's in G1 whiles in G2 the animal underwent the same steps but after suturing the stomach wound and before closing the abdominal wall the site of operation of the stomach wound and also the peritoneal organs were sprinkled with 2gr. of chitosan powder then the wall was closed routinely. Antibiotic therapy was given for all experimental animals for 3 days after operation (penicillin streptomycin combikel® from Kell Company Belgium). Five animals of each group were scarified on 7th and 21st day after operation.

Table, 1: Blaur and Collins scale for the autopsy valuation of the P.O. intraperitoneal adhesions formation.

Grade	Adhesion Description
0	Non
1	fine or slight, easily detachable
2	Thick limited to one area
3	Thick and widespread
4	Thick and widespread adhesion with adhesion of bowels to the anterior and posterior abdominal wall.

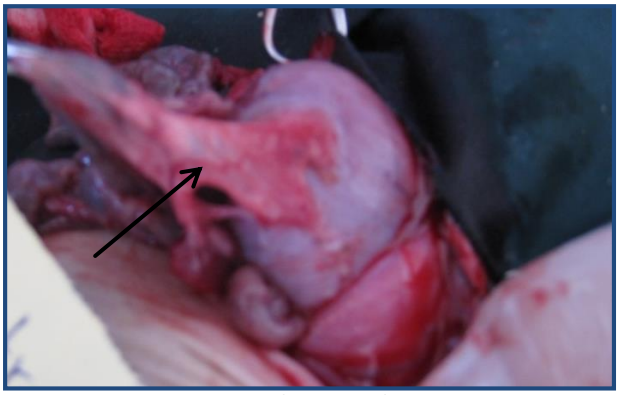
The peritoneal cavity was entered via a reversed U-shaped incision in the anterior abdominal wall, which was retracted caudally to provide maximal exposure and the macroscopic performance for evaluation of intra-peritoneal adhesions and biopsy collections. The quality and quantity grades of adhesions were achieved according to the scoring system which was created by (11) (Table, 1). For histopathological examination of stomach wound in 7th and 21st day of operation, about $3cm^3$ samples were taken and fixed in 10% buffer formalin (12).

Results and Discussion

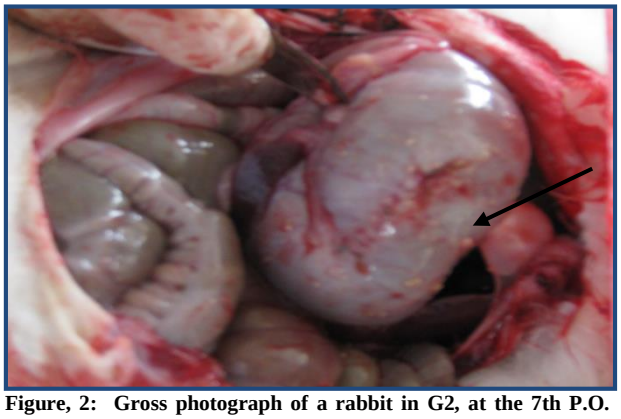
Rabbits of both groups did not show evidence of anesthetic and postoperative complications. At first period 7th day of operation the macroscopic results of G1 revealed severely attached omentum with the site of operation, a large area was attached along the incision (score 4 adhesion) (Fig. 1), the degrees of adhesions in the stomach wound and other internal organs in all cases of this group ranges between score 3 and 4. While in G2, (at the same period) showed no incidence of adhesions at the operation site and also on all abdominal organs (score 0 adhesion), with presence of some remnant chitosan granules in abdominal cavity (Fig. 2). All animals of this group showed the same score (score 0 adhesions). Whilst at second period 21st day of operation at this period the macroscopic result of G1 showed the adhesion at suture line was decreased (ranged between score 2 and 3 adhesions), there was also a wide loosely attached omental adhesion which extends from abdominal wall to the stomach. (Fig. 3), in other case a filmy attachment between a small lobe of liver and visceral surface of the stomach (score 2 adhesion), while at the same period of G2 the gross lesion showed that the incision line had healed without attachments, there is no adhesion neither at suture line, nor in abdominal and pelvic cavities in all animals of this period (score 0 adhesion) (Fig. 4).

At the first week period the histo-pathological findings of G1 showed infiltration of large numbers of dead neutrophils in the subserosal and sub mucosal layers and in between the myofibers (Fig. 5), in addition to proliferation of granulation tissue in the

subserosal layer which showed severe hemorrhage and the blood vessels undergo dilatation with serum protein in their lumina (Fig. 6). While the histopathological section of the G2 at the same period showed infiltration of large numbers of dead neutrophils in the submucosa and in between the myofibers of mascularis with deposition of large amount of fibrin forming fibrin network and presence of remnant of suture material with large number of free RBCs (Fig. 7), where as in other section the submucosal mucus glands undergo cystic dilatation and contain inflammatory cells mainly neutrophils and secretions. Other glands showed hyperplasia of their epithelial lining cells and contain large numbers of neutrophils with cellular debris, and proliferation of granulation tissue in the subserosal layer and extend in between myofibers with presence of remnant of suture materials in the subserosa were also noticed (Fig. 8).

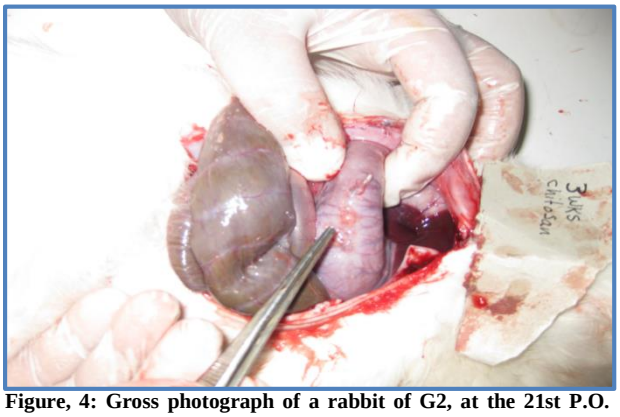


Figure, 1: Gross photograph of a rabbit of G1, at the 7th P.O. day. Showing a strongly adherent thick bands of wide white fibrous adhesions were developed between the wound line of stomach surface with different parts of abdominal structures (score (4) adhesion).

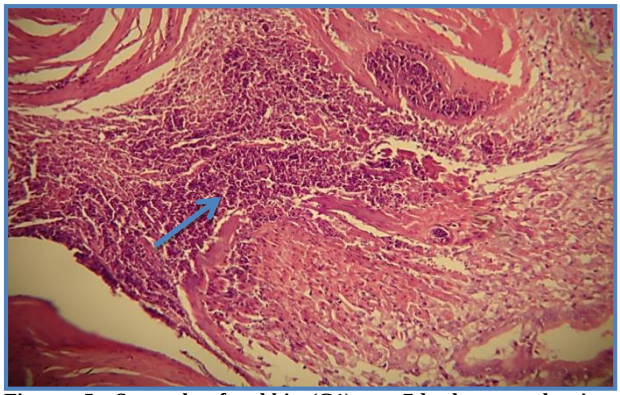


Figure, 2: Gross photograph of a rabbit in G2, at the 7th P.O. day. Showing no adhesions at the operation site and also between all abdominal organs, with presence of some chitosan remnant granules (a row), in abdominal (cavity score (0) adhesion).

Figure, 3: Gross photograph of a rabbit of G1, at the 21st P.O. day. Showing a wide loosely attached omental adhesion extends from abdominal wall to the stomach.



Figure, 4: Gross photograph of a rabbit of G2, at the 21st P.O. day. Showing no any indictable adhesion, the incision line healed without attachments, no signs of adhesion at entire organs of the abdomen cavity.



Figure, 5: Stomach of rabbit (G1), at 7th day p.o showing infiltration of large number of dead neutrophils in the subserosal and submucosal layers and in between the myofibers (blue arrow) (H and E40X).

At the 21 days period; the main microscopic picture at this period of G1 was submucosal edema with infiltration of chronic inflammatory cells mainly mononuclear cells with submucosal and subserosal hemorrhage (Fig. 9), the proliferated granulation tissue undergo myxomatous degeneration (Fig. 10).

In addition to that there is formation of multiple foreign body granulomas containing the remenant of suture material surrounded by large numbers of epithelioid cells with tendency to formation of foreign body giant cells. The granulomas were surrounded by granulation tissue, in addition to focal areas of hemorrhages (Fig. 11). At 21 days post operation of G2; at this period the fibrous tissue contain collagen fibers which are more dense and regular in direction than the previous period and spindle shaped fibroblasts, with few congested blood capillaries containing neutrophils in their Lumina, the infiltration of few mononuclear cells and giant cells were noted surrounding the remnant of suture materials (Fig. 12).

Postoperative adhesion formation in the peritoneal cavity is a fibrotic tissue complaint established by excessive deposition of fibrin during normal wound healing. It is currently believed that a breakdown in the balance between fibrin deposition (fibrinogenesis) and fibrin degradation (fibrinolysis) during wound healing leads to this surgical complication (13). In order to reduce adhesion formation and reformation, an agent must separate damaged surfaces during the fundamental phases of postsurgical repair (14). Chitosan products may act as a biophysical barrier and had the best anti-adhesion potential (15). Chitosan powder used in this investigation led to reduction in the adhesion formation in comparison to the adhesions developed in the rabbits that did not received intraperitoneal chitosan treatment. This result, certainly prove the benefits of this easily used, low-cost and simply prepared antiadhesive agent, also highly agrees with findings by previous researcher on the antiadhesion activity in cardiac surgery, in which they found that chitosan products significantly reduces severity of postsurgical adhesion formation after cardiac surgery in rabbit and pig models (15). Adhesion model in present study was chosen because serosal trauma has been recognized as dependable means of adhesion formation in rabbits, formation of adhesions begins during the inflammatory stage of healing, 24 to 48 hours after the injury, and the adhesions usually are well formed by 5th to 7th day after the injury (16).

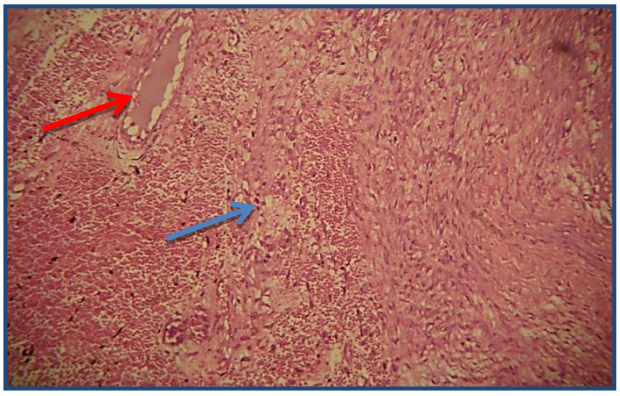
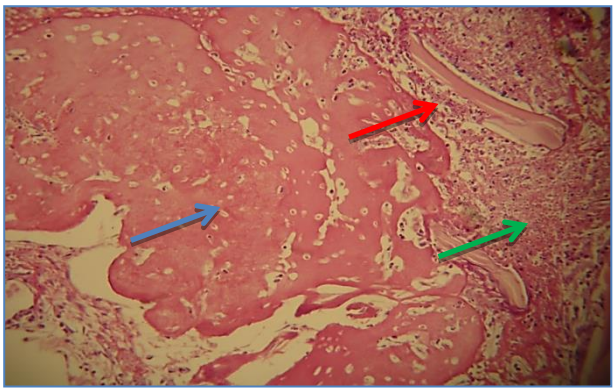
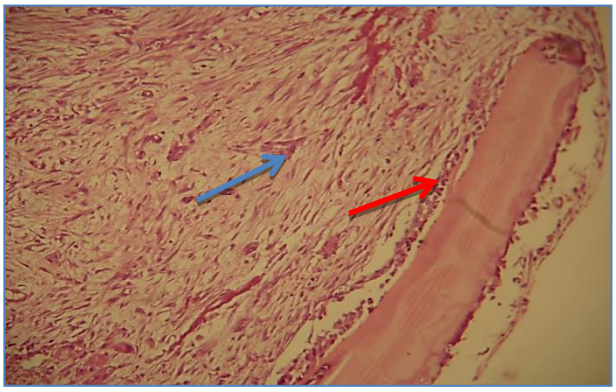


Figure (6): Stomach of rabbit (G1), at 7th day p.o showing sever hemorrhage (blue arrow) and presence of serum protein in the lumina of blood vessels (red arrow) (H and E 20X).



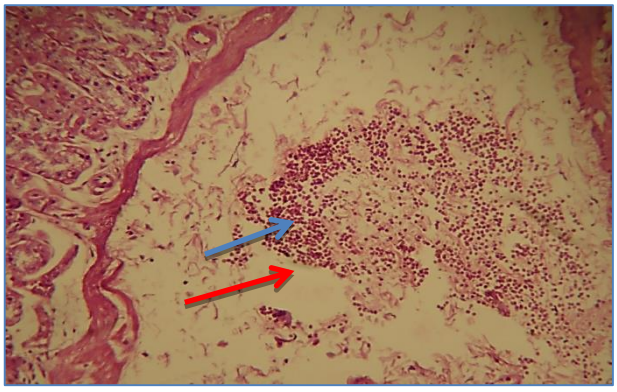
Figure, 7: Stomach of rabbit (G2),7th day p.o showing deposition of large amount of fibrin (blue arrow) with presence of remnant suture material (red arrow) with presence of large number of free RBCs (Green arrow) (H and E 40x).



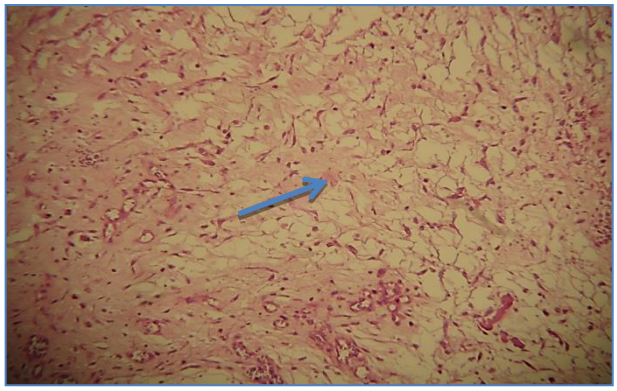
Figure, 8: Stomach of rabbit (G2),7th day p.o., showing proliferation of granulation tissue in the subserosal layer and extend in between myofibers (blue arrow) with presence remnant of suture materials in the subserosa surrounded by few inflammatory cells (red arrow) (H and E40X).

In this study the gross finding in G2 showed no adhesion on the site of operation and also on the adjacent organs, which means that chitosan had improved its effectiveness when applied indiscriminately or randomly without measurements around the injured site, whereas the ease of application of antiadhesion products is an essential factor in outlining the success of their common use. The application of chitosan powder as an effectual single-step

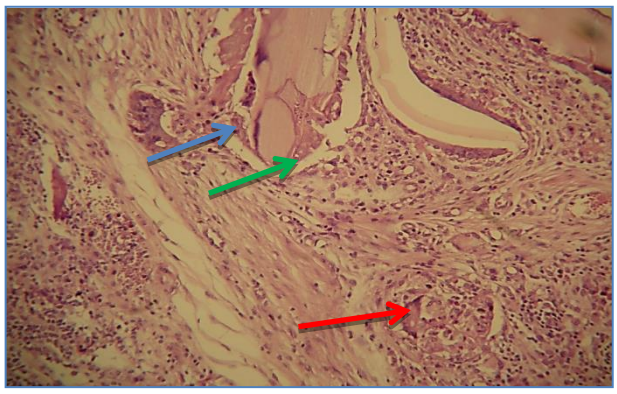
preparation would therefore be of clinical benefit. These finding are important for two reasons. First it is predominantly hard to apply adhesion barrier materials directly on injured sites, especially under condition of laparo-scopic surgery. The capability to apply the powder in the general area of the injured site increases ease of use evidently. It is difficult to know the limits of minor abrasive damage during the operation; there for a product that has some efficacy outside of the area of application would be of clinical benefit (17).



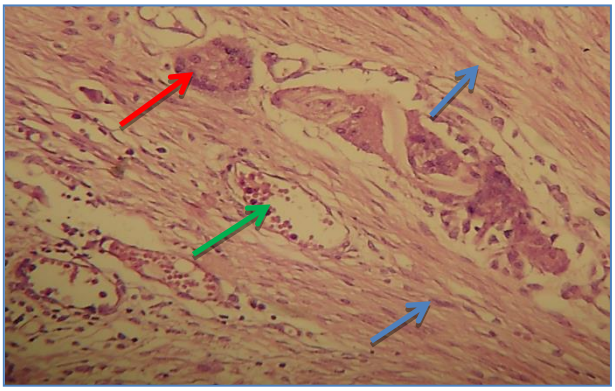
Figure, 9: Stomach of rabbit (G1), at 21st day p.o., showing sub mucosal edema (red arrow) with submucosal and subserosal hemorrhage (blue arrow) (H and E 40X).



Figure, 10: Stomach of rabbit (G1), 21st p.o, showing proliferation of granulation tissue undergo myxomatous degeneration (blue arrow) (H and E 40X).



Figure, 11: Stomach in (G1), 21st p.o, showed foreign body granulomas containing the remnant of suture materials (blue arrow) surrounded by large numbers of epithelioid cells (green arrow) with giant cells formation (red arrow) (H and E 40X).



Figure, 12: Stomach of (G2), 21st p.o. showed dense regular fiberues tissue (blue arrow) with few congested blood capillarries contain neutrophils in their lumina (green arrow) and foreign body giant cells formation (red arrow) H and E 40X.

During surgical procedure in G2 capillary bleeding seems to be arrested after chitosan application. Hemostatic effect of chitosan was reflected by controlling capillary bleeders directly after its application through joining with RBCs by the presence of polycations which are able to form gel heparinized leading to reducing firm coagulum due to negative changes of the cell membrane this agreed with (18) as reduced bleeding also leads to decrease adhesion (19). Although the mechanism accountable for the practical effect of chitosan powder on adhesion formation is unknown, probable theory is that it offers a physical barrier between the injured tissue surfaces. There is sign to suggest that the presence of such a barrier between injured tissue surfaces during early stages of healing limits apposition ,minimizes the deposition of the critically important fibrin matrix, and minimizes adhesion formation (20).

The microscopical results showed enhancement in stages of healing in G2 comparing with G1and this manifestly appear in both examination periods, deposition of large amount of fibrin forming fibrin network in the 7^{th} day of G2 confirm role of chitosan in fibroblast stimulation and tissue organization which comes in agreement with (21). In addition to role of chitosan in attracting the inflammatory cells in early stages especially neutrophil, neutrophilia was accompanied by an increased phagocytosis index. Despite there is a believe that neutrophils cause adhesion formation. But, at the same time, they start the degradation of collagen through the substances released by themselves and through other

undetermined factors (22). It has also been shown that enhancement of macrophages markedly decreases post operative adhesion formation (23). The histopathological finding also revealed presence of fibrous tissue contain collagen fibers which are more dense and regular in direction in 21st day period with presence of spindle shaped fibroblasts, which indicate that the role of chitosan in organization of tissue effect and stimulation of fibroblast this agreed with (24). The use of physical barriers to avoid postoperative adhesion formation has been established in many investigational models (25- 27). A perfect physical barrier should not affect wound healing, should not evoke fibrosis should be stable during the initial stages of adhesion development but degrade later , and should be effective in the presence of blood and body fluid (28 and 29).

It seems that chitosan have or possess all of these properties so it is good wound healing stimulator and this agree with investigators who have before confirmed that chitosan enhance healing in both skin healing model and a large bowel anastomosis model (23 and 30), not induce fibrosis and this is clear in microscopic picture at the both examination period of this study, Conclusion found that chitosan particles are stable and this was reflected by the presence of remaining granules until the 7th day of operation.

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دور الكيتوسان المستخدم موضعيا في تقليل الالتصاقات ما بعد عمليات فتح البطن في الارانب

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الخلاصة

اجريت هذه الدراسة لتقييم قابلية الكيتوسان في منع الالتصاقات داخل تجويف البطن بعد عمليات فتح البطن. استعمل في البحث 20 ارنب سليم سريريا وفي كلا الجنسين وباوزان تتراوح 1.5-2 كغم قسمت عشوائيا الى مجموعتين متساويتين، مجموعة السيطرة ومجموعة المعالجة. اخضعت حيوانات التجربة بعد تخديرها وتحضيرها جراحيا، الى عملية فتح البطن والتي اجريت لاحداث جرح مصلي-عضلي في المعدة بطول 4 سم، اكملت العملية في المجموعة الاولى بخياطة جرح المعدة وكذلك جدار البطن في حين في المجموعة الثانية اجريت نفس الخطوات لحيوانات مجموعة المعالجة ولكن بعد خياطة جرح المعدة وقبل غلق جدار البطن رش (1غم) من مسحوق الكيتوسان داخل تجويف البطن على منطقة العملية وحولها. قتلت خمسة حيوانات من كل مجموعة قتلا رحيما على فترتين (في اليوم السابع واليوم الواحد والعشرين بعد العملية) وبعد اجراء التشريح المرضي فحص التجويف البطني عيانيا واخذت عينات لاجراء الفحص المجهري ولنفس الفترات الزمنية. اظهرت نتائج الفحص العياني والنسجي المرضي وجود فرق واضح بين المجموعتين حيث اظهرت نتائج الفحص العياني عدم وجود الالتصاقات في منطقة العملية (جرح المعدة) وكذلك حول الاعضاء وفي التجويف البطني في مجموعة المعالجة وللفترتين مقارنة مع مجموعة السيطرة التي اظهرت درجات عالية من الالتصاقات في جميع حيوانات السيطرة. ويستنتج من الدراسة ان للكيتوسان دور حيوي في منع الالتصاقات التي تحدث بعد العمليات مع ان آلية عمله غير معروفة لحد الان.

الكلمات المفتاحية: تجويف البريتون، الالتصاقات، الكيتوسان، فتح البطن.