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Research Article

A Prospective, Non-Controlled, Randomised, Clinical Trial of Abdominal Adhesions following Coeliotomy: Do Risk Factors Predispose to Surgical, Physiological and Histopathological Aetiologies? -An Analytical Study in Rabbit Models

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Abstract

Background: Peritoneal adhesions are serious postoperative concern of coeliotomy and other abdominal surgeries, and can result in chronic pain, infertility, or potentially fatal bowel obstruction. Therapeutic and preventive measures have reduced adhesion formation to variable degrees in preclinical studies and clinical trials; however, there is incomprehensible understanding why the incidence of adhesion remains prominent in rabbits and human, at general surgery and gynaecological patients, respectively.

Objectives: We adopted a prospective, non-controlled, randomised clinical trial to study potential risk factors that may predispose to coeliotomy operations, and to discover and analyze whether surgical, physiological and histopathological aetiology plays an influential role in abdominal adhesion formation.

Methods: Thirty female adult rabbits (n = 30) with bodyweight of 1055 - 2910 gm (1965 ± 97.4 gm) and age of 63 - 132 days (111 ± 5.5 days) were subject to this study. The rabbits were randomly categorized into 2 groups; surgical intervention (n = 28) and control group (n = 2). Animals of the surgical intervention group underwent a median coeliotomy, whereas control group had no intervention. On the 10th and 17th postoperative day after surgery, gross observation and histopathological examination were carried out for each wound outcome.

Results: Eighteen (n = 18/28) incisions (64.3%) developed a healthy fibrous scar without any serious complication. Of such incisions, 9 cases (32.1%) were each observed at days 10 and 17. Eight (n = 8/28) cases of abdominal adhesion (28.6%) were seen among the interventional group, of such; 4 cases (14.3%) were presented with adhesions at both days 10 and 17.

Conclusions: Abdominal adhesions may elicit by a synergistic interaction of surgical, physiological and histopathological aetiologies. Genetics, breeds, biomaterials, and technical considerations are questionable of their effects, and arise of an utmost interest to speculate as risk factors.

Keywords: *Abdominal Adhesion; Coeliotomy; Aetiology; Surgery; Physiology; Histopathology; Rabbit*

Abbreviations

CA: California; NZ: New Zealand; POD: Postoperative Day; USP: United States Pharmacopeia; SEM: Standard Error of Means; N: number of Animals

Introduction

Peritoneal adhesions are bands of connective tissue that form between structures in the abdomen and pelvis following surgery, trauma, infection, and other harmful events. Rabbits are known to be exceptionally prone to the development of abdominal adhesions following coeliotomies [1-4]. The omentum in rabbit is lean and often cannot omentalize the viscera satisfactorily. Foreign material such as talc powder leaked from surgical gloves or lint from gauze swabs are risk factors that can induce formation of peritoneal adhesions. Gentle surgical technique with minimal tissue handling is quite essential to prohibit such conditions. Fat necrosis occurs readily in the broad ligament, in particular, where the adipose components decompose into fatty acids and glycerol which combine with ions such as sodium, potassium, and calcium, to generate adherent attachments. Intra-abdominal adhesions are a serious concern and can arise from trauma [1]. These adhesions interfere with gut motility and bladder function, block the ureters, and cause discomfort with variable degrees of pain [4]. Other problems related to adhesions are mostly reflected in postsurgical complications that involve the cecum or colon and result from adhesions to the uterine stump, broad ligament, or ovarian pedicle. Adhesions associated with gastrotomy, enterotomy, and a variety of other gastrointestinal surgeries also occur [3]. The abdominal organs should be handled gently using atraumatic methods. Maintenance of moisture throughout the surgical procedure via repeated irrigation and application of wet sponges is a fundamental precaution to prevent the problem. Any form of chemical irritation (e.g. urine contamination, or inappropriate suture materials such as catgut) should be avoided as these all increase the risk of adhesion. Sterility of the abdominal cavity is crucial to be stipulated in a coeliotomy operation. Any leakage from hollow organs or abscesses must be controlled promptly [2,4]. Necropsy is a key procedure for diagnostic investigation of laboratory animals like rabbits to obtain useful data in clinical and biomedical research [5]. Treatment of adhesions is difficult to determine as surgical breakdown of adhesion can be attempted but reoccurrence is possible. Therefore, prevention of adhesion is of significant importance, taking into consideration the predisposing factors. The objective of our prospective, non-controlled, randomized clinical study is to explore and analyze whether a surgical, physiological or histopathological aetiology predisposes for risk factors which may exacerbate abdominal adhesions in the peritoneal cavity in subsequent to coeliotomy in a translational model of human condition on rabbits.

Materials and Methods

The study protocol was regulated and approved in compliance with animal research ethics set by Assiut University Standards (Faculty Board Decree #22/12/2015). Code of conduct and guidelines on animal use and care were followed as ensued by the Canadian Council on Animal Care [6].

Thirty (30) female rabbits (11 New Zealand and 19 Californian breeds) were randomly admitted to the Small Animal Operation Unit, Department of Veterinary Surgery, Anesthesiology and Radiology, Veterinary Teaching Hospital, Faculty of Veterinary Medicine, Assiut University, Egypt. The rabbits were subject to a prospective study of randomised, uncontrolled, clinical trial. The animals were clinically examined to ensure good health status prior to the experiment.

The rabbits weighed 1055 - 2910 gm (Mean ± SEM; 1965 ± 97.4 gm) and aged 63-132 days (111 ± 5.5 days). The animals were categorized into two groups. Group (I) was assigned as surgical intervention group comprised of 28 animals (12 NZ and 16 CA). Group (II) was allocated as control group, consisting of 2 animals (1 NZ and 1 CA) that had no intervention.

The animals of surgical intervention group were subject to a median coeliotomy operation. The surgery was performed as follows; the abdominal wall layers were aseptically prepared, consecutively incised (on a 7 cm line) and then mass closed by 4 cross mattress sutures using a monofilament thread of polydioxanone USP 3-0 (Unicryl M®, UniMed, KSA) swaged on a ½ circle, 26 mm long, round needle. Each suture was fastened adequately with 4-throw knots (2-1-1-1). The skin was closed as conventionally performed.

Following surgery, a long-acting antibiotic (Alamycin LA®, oxytetracycline 200 mg/ml, Norbrook, UK) was administered as a single intramuscular injection at the dose rate of 20 mg/kg. A non-compressive protective abdominal bandage was applied for one week using sterile gauze. On the 10th and 17th postoperative day (POD) after surgery, gross observation and histopathological examination were carried out following each wound outcome.

The rabbits were sacrificed to obtain histopathological specimens. The abdominal wall specimens were collected, trimmed and fixed in 10% neutral buffered formalin. They were dehydrated in a graded alcohol series, cleared with methyl benzoate, embedded in paraffin wax, sectioned at 4-µm thickness, and eventually stained with haematoxylin and eosin for histopathological examination by light microscopy [7].

Results

Gross examination

In the surgical intervention group, twelve (12) incisions (42.9%) developed a muscular scar of yellowish white fibrous tissue regularly extended along the surgical incision (Figure 1). Of such incisions, 6 cases (21.4%) were observed each on PODs 10 and 17. The suture threads embedded in the peritoneal surface of abdominal wall were invisible in all wounds.

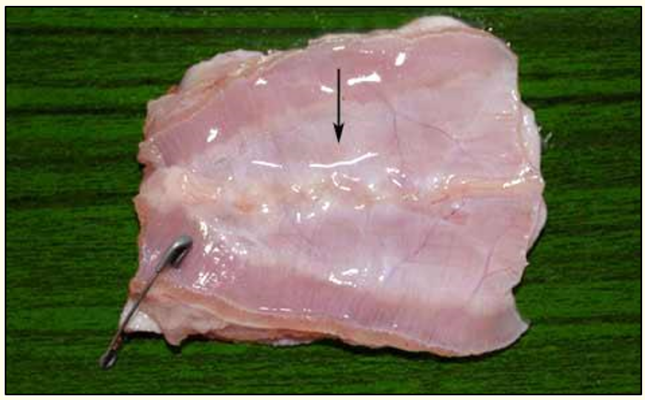

Figure 1: *Gross findings of abdominal wall specimen on POD 10 at the peritoneal surface of the incision showing yellowish white scar formation (arrow) on the area of incised linea alba.*

Six (6) abdominal incisions (21.4%) showed a yellowish white scar tissue on the muscles accompanied with red spots appeared as newly formed blood vessels (Figure 2). Of which 3 wounds (10.7%) were detected at both PODs 10 and 17, and one wound (0.04%) each on POD 10 and 17 was noticed with bluish discoloration diffused at one single side of the incised abdominal muscles.

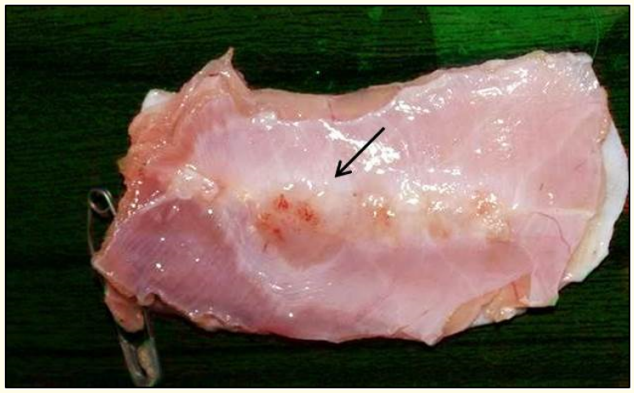

Figure 2: *Gross findings of abdominal wall specimen on POD 10 at the peritoneal surface of the incision showing yellowish white scar formation (arrow) with red spots dispersed on the area of incised linea alba.*

Eight (8) cases of abdominal adhesion (28.6%) were recorded in Group (I), of such; 4 cases (14.3%) were presented with adhesion formation each on both PODs 10 and 17. The adhered tissue was connecting the healed abdominal wall incision with the underlying omental fat (Figure 3).

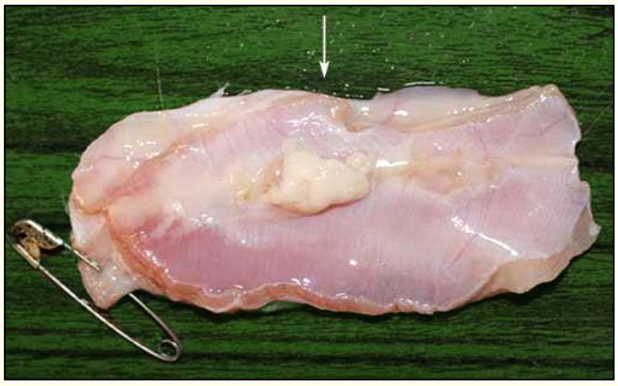

Figure 3: *Gross findings of abdominal wall specimen on POD 17 at the peritoneal surface of the incision showing adhesion formation (arrow) between the peritoneal surface of the abdominal wall and underlying omental fat.*

All (30) animals of the study survived the whole period of experiments except a case of mortality occurred in one rabbit (0.04%) of the surgical intervention group at the day of euthanasia on POD 10. This case was diagnosed with an acute infection of pasteurellosis, confirmed by gross examination and microscopic investigation of direct smears that were collected from the lungs, trachea and abdominal viscera. Postmortem gross examination showed severe congestion and inflammation of the abdominal wall, the two lungs, trachea and one kidney (Figure 4). Microscopic outcomes of direct smears revealed bipolarity of the aetiological microorganisms. Non-exposure to vaccination in this animal under stress of surgery might be a reason behind its susceptibility to an acute illness and further mortality.

Figure 4: *Gross findings of abdominal wall specimen on POD 17 showing abdominal adhesions with congestion and myositis (arrow) around the area of incised linea alba.*

In the surgical intervention group (I) and control group (II), there were no evidence, neither grossly or histopathologically, for any occult herniation or generalized peritonitis in any animal.

Histopathological findings

Rabbit abdominal wall samples with surgical intervention showed engorged blood vessels on day 10 post surgery; this was associated with proliferation of fibroblasts and infiltration of perivascular cuffs with inflammatory cells (neutrophils and monocytes) around the suture tracts (Figure 5).

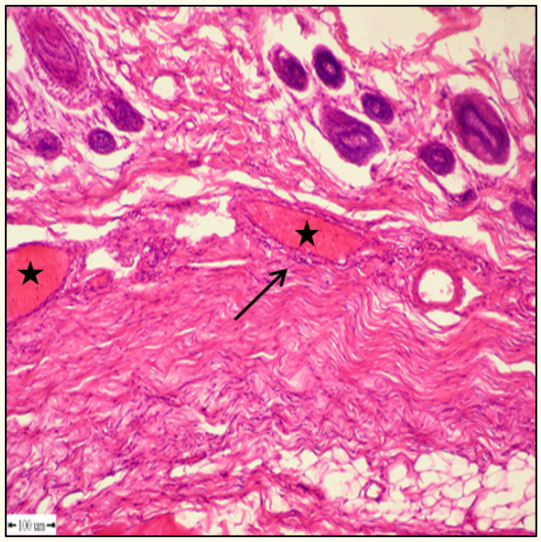

Figure 5: *Photomicrograph of rabbit abdominal wall with surgical intervention on POD 10, showing engorged blood vessels (star) associated with fibroblast proliferation and perivascular infiltration of inflammatory cells around the suture tracts (arrow). H&E stain. Bar = 100 µm.*

Microscopic examination of histopathological specimens of the abdominal wall on day 17 demonstrated adhesion formation between the abdominal wall, peritoneum, and omentum as well as the overlying dermis (Figure 6). Such finding was evident by proliferation of fibrocytes conforming mature connective tissue adjoined to adipocytes, and preceded on POD 10 by aggregations of acute inflammatory cells with mononuclear cells around the suture tracts (Figure 7).

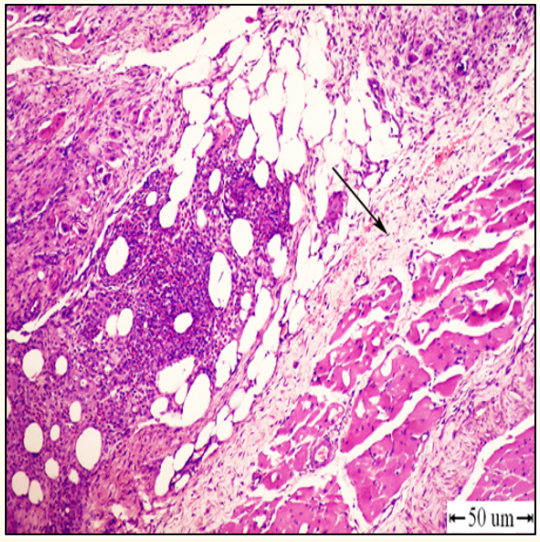

Figure 6: *Photomicrograph of rabbit abdominal wall with surgical intervention on POD 17, showing adhesion formation between the dermis, peritoneum and abdominal muscles (arrow). H&E stain. Bar = 50 µm.*

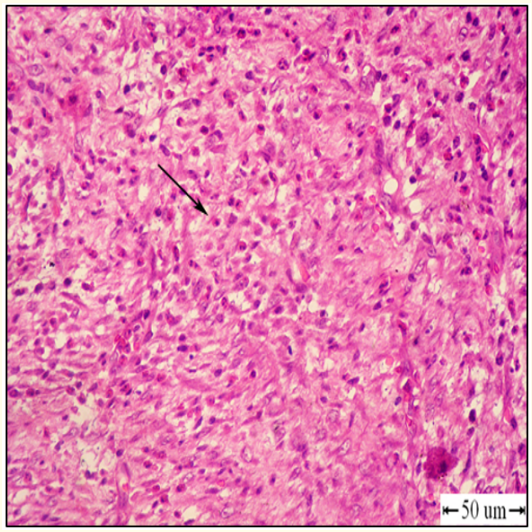

Figure 7: *Photomicrograph of rabbit abdominal wall with surgical intervention on POD 10 showing acute inflammatory cells with mono-nuclear cells (arrow). H&E stain. Bar = 50 µm.*

At day 17 post surgery, there was a notable development of fibrocytosis that has undergone full maturation, and constituted multiple adjacent bundles of mature connective tissue fibers. These were combined with newly formed blood vessels that have grown across the healed surgical incision (Figure 8).

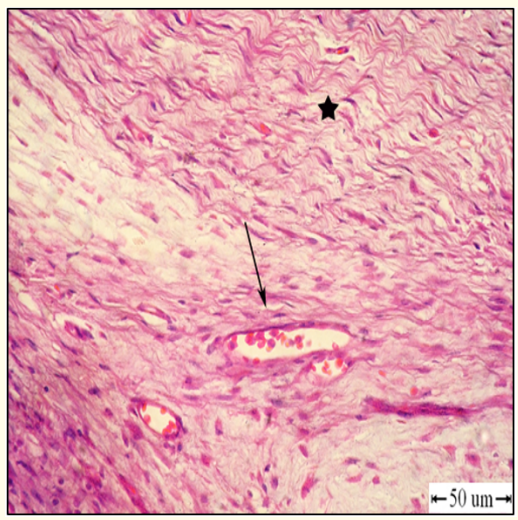

Figure 8: *Photomicrograph of rabbit abdominal wall with surgical intervention on POD 17 showing formation of mature connective tissue (star) and neovascularization (arrow). H&E stain. Bar = 50 µm.*

The gross and histopathological outcomes of the entire studied animals were summarized in table 1 and their findings were sorted out for their respective groups.

Total Study Animal No.	Group Description	Group Animal No.	Normal Scar	Complication		
				Adhesion	Bleeding	Mortality
N = 30	Surgical Intervention	N = 28	N = 18/28 (64.3%)	N = 8/28 (28.6%)	N = 1/28 (0.03%)	N = 1/28 (0.03%)
	Control	N = 2	N = 2/2 (100%)	N = 0/2 (0%)	N = 0/2 (0%)	N = 0/2 (0%)

Table 1: *Summarized random distribution of studied animals for incidence rate of normal and complicated abdominal wall incisions; including adhesion formation, bleeding and mortality.*

Discussion

Abdominal adhesion is one of the major causes of postsurgical morbidity and mortality [8]. Foreign bodies, including suture materials, infection, and bleeding can promote the formation of peritoneal adhesions [9]. A large number of studies have been conducted to determine the optimal protocols for reducing the incidence of adhesions, but no clinically feasible method has yet been established. Efforts have therefore been made to minimize mechanical injury to the peritoneum and to minimize residual blood, bacteria, etc. in the peritoneal cavity by adequate lavage.

Adhesions develop at a high rate following abdominal surgery; as prior reported incidence is 67% in autopsy cases and 93% in cases undergoing abdominal surgery [10]. Due to the heterogeneity and paucity of information on the relative importance of risk factors that predispose to adhesion formation after abdominal surgeries, we adopted a prospective, uncontrolled, randomized clinical trial with scoring complications associated with surgical operations of coeliotomy to point out risk factors that signify incidence rates.

It is important for animal practitioners and gynaecological surgeons to anticipate risk factors in their routine practice to analyze hazards of postsurgical adhesions in individual patients. The risk scores have a similar theme, preoperatively and perioperatively, and the objective is to help both human and animal surgeons to identify their patients at particular risk for abdominal adhesions in a consistent manner, and from this perspective, to make forethought decisions on targeting the use of adhesion-inhibition agents as resources limit their ability to employ them widely. This implies that the surgeon has to adapt their surgical technique as necessary and proper, and decides whether their subjects should receive an adhesion-inhibiting agent based on the physiological state of the patient, and which therapy should be used-considering the type of pathology and surgical procedure to be undertaken-not only fulfilling their duty of care, but also avoiding a potential for medicolegal claim on harm situations [11].

Prevention of adhesions was the topic of many studies involving rabbits as animal models of human disease [12]. A variety of substances have been used to fight against adhesion formation, but most of them have proven to be toxic for use, difficult to apply, possess high complication rate, or simply not to work. Substances such as hyaluronic acid solutions, carboxymethyl cellulose, or chondroitin sulfate can be useful to prevent adhesions [13-15]. Owing to inert nature, these agents act by mechanical separation of surfaces and add a protective "finish" to the viscera [3]. Niles and Williams [16] indicated that is necessary for the abdominal incision to be repaired securely with no tension on the sutures. Closure of the peritoneum or rectus and oblique muscle layers is unnecessary and may contribute to tissue ischemia in these layers, and may increase the risk of abdominal adhesions.

Experimental studies have shown that the size of the suture material is more important than tissue reactivity in adhesion formation [17]. Thus, the choice of fine suture material as well as a principled surgical intervention is substantial to minimize adhesion formation in rabbits. Small gauge (3-0, 4-0 or 5-0) modern suture materials swaged on needles are favourable. Polydioxanone (PDS) or poliglecaprone (Monocryl) can be used for most situations [1]. Because the holding layer of the abdominal wall is mainly the fascia, it should always be incorporated in the sutures. Enclosing the peritoneum in the sutures is controversial. In dogs, suturing the peritoneum could increase the incidence of postoperative intra-abdominal adhesions [18]; however, according to an experiment in rabbits, the closure of the peritoneum results in lower chance of adhesion formation. Whitfield., *et al.* [19] have determined whether adhesions to the peritoneum beneath the anterior abdominal wall incision could be lessened by peritoneal closure using less-reactive suture material. The findings showed that peritoneal closure reduced adhesion scores, compared with peritoneal non-closure, regardless of the type of suture. While no particular

suture is superior to date, polygalactin, however, resulted in the least chronic inflammation and fibrosis. Frequency of adhesion formation to coeliotomy wound in response to absorbable/non-absorbable sutures and mass/layered closure techniques were studied by Ansari [20] comparing polyglactin and polyamide, respectively, in both mass and layered closure technique of 10-cm paramedian coeliotomy incision in 48 rabbits. Layered closure with polyglactin has developed maximum number of adhesions to laparotomy scar. In contrast, a recent study on rats, the incidence of adhesions under clean conditions was lower for polyglactin than for polydioxanone. The incidence of adhesions did not differ among four different types of sutures (Silk, PDS, Vicryl, Monocryl) under contaminated conditions; but the incidence of severe adhesions was significantly higher for polydioxanone than that for any of the other sutures. These results may be attributed to the use of a relatively thick (USP 3-0) suture and long-term retention of polydioxanone as slowly absorbable monofilament, resulting in protrusion of the cut ends of the ligated suture into the peritoneal cavity even at 2 weeks and possibly causing mechanical injury of the surrounding tissue. Polydioxanone, which retains its tensile strength for a relatively long period, is suitable for use at sites where long-term preservation of the wound is needed (e.g. in cases of abdominal wall closure) [21]. In our study, it was found that polydioxanone sutures were invisible and completely embedded in the muscular tissue; this calls into our understanding that there have been ambiguous factors that could induce adhesion formation.

Although the use of interrupted cross mattress suture for closure of the skin wound after coeliotomy is strong enough to avoid wound dehiscence, the technique carries inevitable disadvantages based on the results of a prior experimental study [22]. One of these was impaired wound healing in two infected wounds (8.3%) confirmed by the histopathological findings that showed acute inflammatory reaction and presence of dead neutrophils within the scab. The advantages of the cross mattress technique in cutaneous closure have yielded (i) very good cosmetic appearance on the 17th postoperative day. This was in consistence with Kumar., *et al.* [23] and Islam., *et al.* [24] who found similar outcomes in cattle. They stated that cross mattress, as a tension suture, is stronger than simple interrupted sutures, and it brings the tissue into close apposition without excessive eversion of the wound edges. Moreover, in the present study, (ii) the cross mattress suture pattern itself was successful in the abdominal wall closure since no incisional herniation, occult herniation, eventration, or generalized peritonitis have been detected in any of the surgical intervention group. Kailas and Chandrashekar [25] were harmonious with these findings, and they concluded that interrupted x-suture technique using polydioxanone for closure of midline laparotomy incision is superior to prevent major complications like burst abdomen, wound infection and suture sinus.

In the current study, it is believed that the mass closure of peritoneum immediately beneath coeliotomy incisions results in comparable adhesion rates (28.6%). Adhesion formation could not be reduced further using less-reactive or inert sutures. In this study, polydioxanone suture was used in 28 rabbits undergoing surgical intervention, and it is open to question whether this monofilament suture is likely to play a prime role in adhesion. Polydioxanone is a slowly degradable polymer with hydrophobic properties (lasting 6 - 12 months for complete loss) [26]. Diverse materials have been tested within the peritoneum in previous studies. While there can be little doubt that some materials control the rate of drug release more effectively than others, scarce knowledge has been published on antibiotic drug delivery in the peritoneum; suggests that most materials that have been used as barriers to adhesion have the potential to be used as drug delivery systems. As we have seen, some have been tried [27,28], although so far none have into translated clinical practice in regard to oxytetracycline, as a drug of choice for a majority of veterinary practitioners. Whether the converse is true, i.e. whether the more hydrophobic polymers used for conventional drug delivery are compatible as intraperitoneal barriers, remains to be proven. Since the initial efforts to prevent postsurgical adhesions were made more than a century ago [29], a range of anti-adhesive devices have been used, but their efficacy and the scope of application still remain limited. Adhesion formation continues to be a challenge in peritoneal surgery. However, given the accumulated knowledge from research and clinical experience, and with recent advances in tissue engineering and drug delivery technology, there is a reason to be optimistic that complete prevention of postsurgical adhesions is an endeavor that can be achievable in rabbits since their peritoneum is absolutely delicate [8].

The pathogenesis of adhesion formation is complex, with many factors involved. The processes of fibrinous adhesion, fibroblast invasion and collagen deposition play a critical role in the formation of postsurgical adhesions [8,30]. Histopathological studies demonstrate a clear series of events from injury to the formation of adhesions. Abrasions and other trauma in surgery lead to disruption of the peritoneal mesothelium and fibrin is then released with a cascade of elements, including leukocytes and mesothelial cells. The fibrin is deposited at the damaged surface as a consequence of bleeding and post-traumatic inflammation. During wound healing, fibrin deposits from

damaged mesothelium enlarge to form a bridge between opposing tissue surfaces. Locally generated fibrinolytic factors are released that may degrade all or part of the fibrin bridge. However, surgery, infection and hypoxia reduce fibrinolytic activity and, under these circumstances, fibroblasts and other cells may migrate across the bridge remnants transforming it into an adhesion [11,31].

The process of adhesion formation commences from the moment of peritoneal injury during surgery, as a result of which the inflammatory cascade is triggered. While the severity and extent of adhesions may alter over weeks or months, the question of whether or not an adhesion develops at all is determined in 3 - 5 days after peritoneal trauma takes place, this is to mean; after surgery has been carried out [32]. During such period, the fibrin layer is diminished through fibrinolysis and the peritoneal membrane either becomes fully re-epithelialised or not. If fibrinolysis does not proceed, an irreversible tissue bridge (adhesion) develops, which strengthens within the following weeks and months and in which blood vessels and nerve fibres may grow [33]. In the current study, the developing yellowish white fibrous tissue scars with red spots have been grossly and microscopically observed on the peritoneal surface of the abdominal muscles, and these could be interpreted as newly formed minute blood capillaries which imply the expression of angiogenesis with notable tissue perfusion as an initial delayed step for further adhesion formation.

In this study, abdominal adhesions occurred at an equal rate of incidence for New Zealand and Californian breeds of rabbits. The interaction of the acute-phase inflammatory cascade is still not fully understood in human, nor is its role in changing gene expression patterns and regulating both normal and adhesion fibroblast proliferation [34]. There is no specific time for rabbits to be in oestrus with notable signs of heat. After they reached sexual maturity (3.5 to 4 months for small breeds), they can be in heat at any time during the year. This is the same for both male and female rabbits. Female rabbits may undergo some period of oestrus where their fervency during heat will be greater or lesser. However, when this time will be is almost impossible to predict. Just as in the female cat, rabbits are induced ovulators; which means no ova will result unless mating occurs. While this induction by copulation was not the case in any rabbit of the whole study and since all animals were intact, the current researchers believe that a hormonal factor of oestrus may be ruled out. As in other rodents, oestrus cycle existing in the rabbit can be observed by the vaginal smear method, though the indication of oestrus is rather obscure than that of other rodents. In the rabbit, three different histological pictures can be presented by a vaginal smear, but only the nucleated epithelial cells may be used as a criterion for the heat stage. When estradiol levels are low, this can lead to fibroblast proliferation and synechiae formation in Asherman's syndrome [35]. In contrast with these great interests, little is known about the process of synechiae and its physiopathology. Meanwhile, this could help in developing effective preventive treatments for abdominal adhesions.

Adhesion formation is a multigenic phenomenon and the role of different activators and factors in this complex process is a matter of plentiful research, pursued for not only improving our understanding of the development of adhesions, but also, most importantly, finding optimal strategies for adhesion prevention. The most promising avenues of research are strategies to separate damaged peritoneal surfaces, the fostering of the process of fibrinolysis and the regulation of ischemia and prevention of angiogenesis. While the latter approaches are currently still only a research hope, the former is already an available option that surgeons can consider in their clinical practice.

Conclusion

The current study suggests that postoperative intraperitoneal abdominal adhesions may develop through a sophisticated, complex, and synergistic interaction of surgical, physiological and histopathological aetiologies. Genetics, breeds, biomaterials, and technical considerations are questionable of their impacts, and these may arise of a paramount interest to anticipate as potential risk factors.

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Conflict of Interest

The authors declare no conflict of interest.

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