The effect of *Aloe vera* gel on experimentally induced peritoneal adhesions in rats

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**SUMMARY**

The accelerate effect of *Aloe vera* gel in the wound healing process is known. Because peritoneal healing is a kind of wound healing process, it was hypothesised that post-operative peritoneal adhesions (PPA) may be reduced with intra-peritoneal *Aloe vera* gel administration.

The study was conducted with 45, 6-month-old, out-bred female Sprague-Dawley rats with a mean weight of 236 ± 17 g. The rats were divided into three equal groups. An adhesion model was constituted in the caecum and terminal ileum of all rats in each group. After above process, the sham group received no further treatment. The remaining rats received a 5 mL intraperitoneal injection of either saline (NaCl 0.9%, control group) or *Aloe vera* gel (treated group) before the abdomen was closed. Ten days later, rats were sacrificed and the adhesions were graded according to their degree of severity. The mean adhesion score of *Aloe vera* gel treated rats was 3.0 ± 2.3 while it reach 10.2 ± 4.6 in the sham group and 9.6 ± 4.2 in the control group. This study strongly suggests that intra-peritoneal *Aloe vera* gel administration can reduce PPA in rats.

**Keywords** : Surgery - peritoneal adhesions - *Aloe vera* gel.

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**RÉSUMÉ**

L’effet d’un gel à base d’*Aloe vera* sur les adhésions péritonéales expé- mentalement induites chez le rat. Par N. KILIÇ.

Les propriétés favorables à la cicatrisation du gel d’*Aloe vera* sont bien connues. Nous avons fait l’hypothèse selon laquelle les adhérences périto- néales post-chirurgicales peuvent être réduites par l’administration intrapé- ritonéale de gel d’*Aloe vera*.

Cette étude a été réalisée chez 45 rats Sprague-Dawley âgées de 6 mois et dont le poids moyen était de 236 ± 17 g. Les rats ont été répartis en 3 groupes. Un modèle expérimental d’adhérences péritonéales a été appliqué à tous les rats au niveau du caecum et de l’iléon terminal. Au cours de l’in- tervention, les animaux du groupe témoin négatif n’ont pas été traités. Les autres rats ont reçu une application intrapéritonéale de 5 mL de sérum phy- siologique (groupe témoin positif) ou d’un même volume de gel d’*Aloe vera* (groupe traité). Dix jours après l’intervention, les rats ont été sacrifiés et la sévérité des adhésions a été notée. Le score moyen des adhérences du groupe traité au gel d’*Aloe vera* a été de 3.0 ± 2.3 alors que ce score a atteint 10.2 ± 4.6 dans le groupe témoin négatif et 9.6 ± 4.2 dans le groupe témoin posi- tif. Les résultats de cette étude suggèrent fortement que le gel d’*Aloe vera* appliqué intrapéritonéalement peut réduire les adhérences post-chirurgi- cales.

**Mots-clés** : chirurgie - adhérences péritonéales - gel d’*Aloe vera*.

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**Introduction**

Peritoneal adhesions are defined as pathological fibrotic bands developed between any surfaces in the peritoneal cavity. For the development of adhesions between two surfaces inside the peritoneum, there must be peritoneal mesothelial damage on at least one surface [23]. A few hours after the mesothelial damage, fibrinous exudate is constituted. When the exudate is absorbed, fibrous bands and newly formed capillary vessels remain at the site and these structures form the permanent fibrotic adhesions [23,32].

Post-operative peritoneal adhesions (PPA) develop after 53 to 90% of all laparotomies in humans [15,16,28] and animals [4,9]. Intestinal obstruction related to PPA develops in 1% of all surgical interventions and in 3% of all laparotomies [11]. Enterocutaneous fistuli, intra-abdominal abscesses, ureteral obstruction, and chronic abdominal pain may also develop as a result of PPA [15]. Several agents have been developed to solve this very serious problem of abdominal surgery [1,15,38].

*Aloe vera* (L.) Burm. f., (Liliaceae) has been used in the traditional medicinal practices of many cultures for a host of curative purposes. *Aloe vera* gel has been applied topically by ancient and modern cultures throughout the world for its anti-inflammatory and wound healing properties. It has been used in the treatment of a variety of disorders including wounds and burns [19]. The fresh gel, juice or formulated products have been used for medical and cosmetic purposes, as well as for general health.

There is no agreement about how to prevent adhesion formation and, what to use, adjuvants or barriers or any other method. For these purposes corticosteroids and non steroid anti-inflammatory drugs had been used frequently [1,15,38]. Modulation of the immune response to peritoneal injury may prevent postoperative adhesion formation [3]. *Aloe vera* has a number of properties ascribed to it : tissue penetration, topical anaesthesia, antimicrobial activity, anti-inflammatory and immunomodulating function [10,19,21,22,40]. Because of anti-inflammatory and immunomodulating properties, we decided to investigate the effect of *Aloe vera* gel on the prevention of intraperitoneal adhesions.

**Materials and methods**

**GENERAL.**

The *Aloe vera* gel was obtained by Forever Living Product (Arizona, USA). The study was conducted in Adnan Menderes University Faculty of Veterinary Medicine,
Experimental Animal Raising and Research Laboratory. The rats were also obtained from this laboratory. Forty-five female rats of the Sprague-Dawley included in the study were 6-month-old, out-bred, female rats of 236 ± 17 g. They were kept in breeding cages of 40 cm x 30 cm x 20 cm in size with plastic walls, the floor covered with wood shavings, and a fence with wire on the roof. A maximum of five animals were kept in one cage. They were fed with a pellet food manufactured specially for rats and water supplied with a drinking bottle. Following overnight fasting all animals were anesthetized by putting them in an ether jar for about 1-1.5 min until they became stupied and anaesthesia was maintained with intraperitoneally 10 mg/kg xylazine (Alfazyne, Egevet) and 75 mg/kg ketamine (Alfamyne, Egevet). The mid-abdominal area was shaved and prepared with povidone iodine.

The peritoneal cavity was entered through a 3-cm midline incision. The terminal ileum and cecum of all animals were mobilised and placed onto wet gauze. Both sides of a 10-cm terminal ileum segment, just proximal to the caecum, and caecum were scraped until there were serosal petechiae on the intestinal surfaces. Later the arteries of the scraped segments were clamped with a microbulldog clamp for 1 min to induce transient ischemia (scraping model) [14].

After above process, the animals were randomly allocated into 3 groups. The sham group (n=15) had no further treatment. The remaining rats received a 5 mL intraperitoneal injection of either NaCl 0.9% (control group n=15) or Aloe vera gel (treatment group, n=15) before the abdomen was closed. The abdominal incision was then closed in two layers with continuous 3-0 propylene suture. The animals were then placed on the regular pellet (state manufacturer) food. Ten days later, the rats were sacrificed with an overdose of ketamine and the peritoneal cavities were entered with a reversed U-shaped incision of the anterior abdominal wall, which was retracted, caudally to provide maximal exposure. A blood sample of 2 mL was taken by cardiac puncture from the rats for biochemical and haematological analysis.

The protocol was performed with the approval and under the supervision of the Ethics Committee of the University of Adnan Menderes.

EVALUATION OF ADHESION FORMATION.

The abdomen was completely opened for the assessment of adhesions. Two observers blinded to the animals group assignment separately assessed number and severity of adhesions using a well-documented adhesions severity scoring system. For this purpose the classification of NAGELSCHMIDT et al. [33] was applied, with the following modifications. Single adhesion strands were counted and graded on a scale of 0-4: with no adhesions, grade 0; fine filmy adhesion easy to separate from the tissue, grade 1; dense adhesion which can only be divided by tension, grade 2; adhesions which cannot be separated by tension without injury of the serosal layer, grade 3; adhesions in a conglomerate with the intraperitoneal organs, impossible to be divided and counted, grade 4. For grade 4 adhesions, 15 points were given.

The biochemical and haematological parameters were compared between groups with the Mann-Whitney U test.

### Results

Table I and Figure 1 show the results of adhesion assessment. The mean adhesion score of Aloe vera gel treated rats was 3.0 ± 2.3 while it reach 10.2 ± 4.6 in the sham group and 9.6 ± 4.2 in the control group. Mean values of albumin and hemoglobin serum levels, and mean leucocyte counts in the blood are given in Table II. No significant differences among the groups were found with regard to albumin, hemoglobin levels, and leucocyte counts.

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**Table I** — Individual and mean (±SD) adhesion scores of the rats from the sham, control and treatment groups.
Thus, both large and small peritoneal defects healed equally fast. Although the process of regeneration of the mesothelial surface of the peritoneum has been investigated extensively, it is not completely understood for several reasons, including interspecies differences in peritoneal physiology, limitations of animal models, and the complexities of interperitoneal circulation and transperitoneal transport. However, most researchers agree on certain basic facts based on animal research [16,19,23,31,36]. In this study, we have chosen the rat as an animal model.

Peritoneal adhesions are classified into three categories—congenital, inflammatory, and postoperative adhesions—according to their mechanisms of formation. Several mechanisms have been proposed for the development of inflammatory and postoperative adhesions, and many factors have been described. Among these factors, the most important ones are peritoneal injuries, infections, and foreign bodies left within the abdominal cavity [15,16,36]. Also, ischemic lesions formed on peritoneal surfaces are accepted as one of the most important factor in adhesion formation [16,36].

There are many experimental models for engendering peritoneal adhesions: the damaged uterine horn model, the ileal transection model, the large bowel anastomosis model, the peritoneal damage model, the bacterial peritonitis model, and the scraping model [8,24,25,34]. The scraping model is very effective in engendering peritoneal adhesions because there are two stages in the damage: direct mechanical intestinal wall damage from gauze scraping until petechial points appear, plus ischemic damage which is secondary to vascular clamping. For that reason, this model, which mimics abdominal surgery, has been chosen in this study. Preoperative anaesthesia was administered intraperitoneally; this technique neither prevented inflammation sufficiently to inhibit adhesion formation in control animals nor induced inflammation sufficiently to cause adhesions distant from the surgically manipulated site.

Clinical and experimental studies show that the frequency of adhesion development after abdominal operations is very high. A most definitive work made on postoperative adhesion frequency is the *post-mortem* study carried out by WEIBEL et al [42] on a large cadaver series. Frequency of adhesion in the cadavers, which had undergone previous abdominal operation for various reasons, was determined to be 67% in their work.

Innumerable substances and methods have been used, either locally or systemically in an effort to reduce or prevent PPA formation, such as sodium citrate, heparin, dextran, pro-stigmme, carboxymethylcellulose, olive oil, honey, steroids and antihistamines [15]. Intra-abdominal infusion of high molecular weight solutions and application of temporary physical barriers act by mechanically separating peritoneal and serosal surfaces during early healing. In an experimental study, BOTHIN et al. [5] showed that the bacterial flora plays a significant role in adhesion formation especially around the surgical anastomosis. Adhesion formation after visceral or parietal injury is a dynamic process with distinct stages. Peritoneal injury causes the accumulation of an inflammatory exudate that leads to fibrin deposition [32] resulting in fibrinous adhesions between adjacent organs. The fate of these adhesions depends on the fibrinolytic capacity [6,20,38,41]. If the peritoneal injury is minor and mesothelial cells are largely intact, equilibrium between fibrino- genesis and fibrinolysis is achieved and healing without permanent adhesions develop. If the peritoneal injury is severe, the underlying connective tissue is exposed and normal serosal fibrinolytic activity disappears [36]. Damaged mesothelial cells induce the emergence of endothelial and inflammatory cells that produce plasminogen activator inhibitor that

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**TABLE II.** Mean (±SD) serological and hematological parameters of the rats from the control (saline) and treatment groups. The rats from the treatment group received an intraperitoneal application of *Aloe vera* gel while saline was administrated to rats from the control group.

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<th>Groups</th>
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<th>Treatment group</th>
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<tr>
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<tr>
<td>Albumin, g/dL</td>
<td>3.84 ± 0.32</td>
<td>3.96 ± 0.51</td>
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<tr>
<td>Hemoglobin, g/dL</td>
<td>12.5 ± 2.1</td>
<td>11.9 ± 2.7</td>
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<td>Leukocytes/ mm³</td>
<td>6.39 ± 0.95</td>
<td>6.23 ± 0.65</td>
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**FIGURE 1.** — Mean (±SD) adhesion scores of the rats from the sham (no treatment), control (saline) and treatment groups. The rats from the treatment group received an intraperitoneal application of *Aloe vera* gel while saline was administrated to rats from the control group.

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**Discussion**

With the advent of more sophisticated anaesthetic and surgical techniques, abdominal surgery for the treatment of intestinal obstruction or strangulation in horses has become commonplace. Unfortunately, the clinical importance of intra-abdominal adhesions concurrently has become more apparent [4,9,15]. Recurrent bouts of colic associated with intra-abdominal adhesions often necessitate additional surgery or euthanasia. Fortunately, in contrast to humans and horses, adhesions occur infrequently in small animal surgical patients and rarely cause intestinal obstruction [9].

Adhesion prevention models are essential and important for determining the success of various methods of adhesion prevention. Most of studies associated with adhesion have been performed with animal models. Using a rat model, ELIIS [16] established for the first time that, unlike dermal defects, both large and small peritoneal defects healed equally fast. Although the process of regeneration of the mesothelial surface of the peritoneum has been investigated extensively, it is not completely understood for several reasons, including interspecies differences in peritoneal physiology, limitations of animal models, and the complexities of interperitoneal circulation and transperitoneal transport. However, most researchers agree on certain basic facts based on animal research [16,19,23,31,36]. In this study, we have...
decreases functional fibrinolytic activity [16,30,32]. Low fibrinolytic activity allows the evolution of fibrinous adhesions towards organised permanent firm adhesions [32].

Mechanical separation of the peritoneal surfaces used either organic (ox peritoneum) or bioabsorbable inorganic membranes [1]. But, unfortunately these materials and procedures had only limited success in abdominal surgery.

Several researchers have used different criteria for grading adhesions [17,18,24,29,31]. The Nagelschmidt model grades adhesions as 0-4 according to their severity [33]. It was adopted the Nagelschmidt model in this study because of its simplicity and rationale. Aloe vera gel has been used in many medical research studies for many purposes especially in recent years, but it has never previously been tried in preventing PPA. With several ingredients and specific properties, Aloe vera gel a broad spectrum of effect: it has antifungal and antimicrobial activities, anti-inflammatory effects and promotes wound healing [2,21,22,26,29,39].

In this study, we have chosen Aloe vera gel for its broad spectrum of effect especially its positive influence on the content of collagen and its characteristics in a healing wound, which substantiates its use as a wound healing agent. Aloe vera has been shown to heal wound faster when used as a crude gel [10,11,29] or as a formulated product [22]. Many components of the gel have been proposed to contribute to wound healing property of Aloe vera, the main component being the gel polysaccharides [19]. Recent studies have shown that treatment with mannose-6-phosphate [11] and acemannan [35] from the Aloe vera gel resulted in faster healing of wounds. Analysis of various extracts of the lyophilized Aloe vera gel has shown that the alcohol extract was capable of increasing collagen biosynthesis in wound tissues. Recently, VAZQUEZ et al. [39] have studied the anti-inflammatory activities of the Aloe vera gel and reported the presence of saponins, naftaquinones, antraquinones, sterols and triterpenoids in alcohol extract. As the peritoneal fluid is not in constant contact with the peritoneal surface, the cellular mediators that exist in the peritoneal fluid reflect the biochemical dynamics of adhesion formation. Evidence from current literature suggests that pro-inflammatory cytokines such as interleukin (IL)-1, IL-6 and tumour necrosis factor (TNF)-α are released into the abdominal cavity after abdominal surgery [3,7]. These cytokines may play a role in adhesion formation/reformation. Pro-inflammatory cytokines may be involved in adhesion formation/reformation in a number of ways: IL-1 and TNF-α are both pro-inflammatory cytokines important in the early phase of wound [27], and are produced by activated macrophages in the peritoneal fluid [3] whereas IL-6 is expressed by activated macrophages and its production is up-regulated by IL-1 during the inflammatory process [7]. Both IL-1 and TNF-α are potent inducers of IL-6. These cytokines are thought to be important as they interact extensively with the fibrinolytic pathway and contribute directly or indirectly to the remodelling of the extracellular matrix (ECM) [7]; the abnormal control of ECM remodelling may be responsible for the formation of adhesions after peritoneal injury [12,13,37]. The effects of Aloe vera on microcirculation and levels of TNF-alpha and IL-6 were investigated in rats after inducing burn [13]. It was found that the amount of leukocyte adhesion and the levels of TNF-alpha and IL-6 were significantly reduced in the treated rats. Aloe vera could inhibit the inflammatory process following burn injury, as suggested by the reduction of leukocyte adhesion, as well as pro-inflammatory cytokine levels.

In this study we observed that covering the peritoneally damaged cecal and terminal ileal surfaces with Aloe vera gel significantly decreases the development of PPA. We suggest that three mechanisms could be involved in this effect: (i) an increased healing process due to its antimicrobial activity, anti-inflammatory and immunomodulating effects following absorption of Aloe vera; (ii) the inhibition of mechanical contact between the surfaces and (iii) the inhibition of the inflammatory process resulting from the reduction leukocyte adhesion and proinflammatory cytokines.

References

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