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Studying the Effect of Local Solution of Clobetasol on Peritoneal Adhesion after Laparotomic Surgery in Rats

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Authors' contributions

This work was carried out in collaboration between all authors. Authors SN, LG, HB and AM designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors NSM, SAM and SN managed the analyses of the study. Author SN managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background and Objective: Adhesion is an important complication of abdominal and pelvic surgery. Applying corticosteroids reduces vascular permeability and releasing of cytokines and chemotactic factors. The current study has examined the effect of clobetasol solution on intra-abdominal adhesion in the rat after laparotomy.
Materials and Methods: 50 albino male rats with age of three months were undergoing laparotomy; the ileocecal abrasionas induced the peritoneal adhesion. The rats were randomly divided into 5 groups (10 rats per group): the first group was treated with 5 ml clobetasol 0.05%; the second group was treated with 5 ml clobetasol 0.025%; the third group was treated with 5 ml clobetasol 0.0125%; the fourth group was treated with 5 ml paraffin and fifth group (control) was no undergone under any treatment. After 14 days, the adhesion and histopathologic changes were compared between the groups. The rats that died for any reason were excluded from the study.
Results: From among 50 rats, 3 rats died in groups 3, 4 and 5. There was a significant statistic

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difference between the groups regarding adhesion severity (p = 0.018). In the case of integration of intervention groups (groups 1 to 3), there was a significant statistic difference in the amount and severity of adhesion, as well as the rate of inflammation and the extent of fibrosis among the groups (p = 0.028, p = 0.03, p = 0.002, p = 0.048) which was determined by Fisher's exact test.
Conclusion: The clobetasol solution can prevent the onset of adhesion after laparotomy in mice and reduce its intensity. Safety and the possibility of using clobetasol to prevent adhesion after abdominal surgery in humans require more clinical trials.

Keywords: Peritoneum; adhesion; laparotomy; clobetasol.

1. INTRODUCTION

Adhesion or band or fibrosis tissue refers to the formation of a non-elastic bar between two intraperitoneal organs, following the surgical trauma of the peritoneum. The peritoneum is a serous membrane in the body and its area is slightly more or slightly less than the skin surface and includes mesothelium layer and vascular stroma [1].

The repair process of the peritoneum following a surgical trauma is a serious concern for surgeons. Based on the mechanism of peritoneal restoration the peritoneal mesothelium cells are re-mesothelialised in the place where a defect occurs [2]. Peritoneal trauma leads to the release of vasoactive quinine and histamine. Consequently, the passive fibrinogen is turned into active fibrin, which in turn causes the formation of a fibrin matrix. The fibrin matrix causes the two damaged layers of the peritoneum to adhere. At this stage, a fibrinolytic activity results typically in the decomposition of fibrin matrix and loss of adhesiveness. If the local fibrinolytic activity is not sufficient, the formation of the fibrin matrix increases and, as a result, it becomes fully adhesive [3,4].

Peritoneal adhesion is a global problem and may be seen after abdominal or pelvic surgery. Adhesions cause a wide range of disorders and diseases and lead to many intestinal obstructions and peritonitis after surgery [5].

55-94% of patients with open surgery have a chance of adhesion [6]. Re-admission of 50% of patients who have been exposed to surgery is due to disorders associated with adhesion [7].

In human models, the post-operative adhesion prevention process consists of three strategies: First, the laparoscopic surgical procedure compared with laparotomy [8]; Second, the microscopic surgery technique [9] and third, the surgical interventions including fibrinolytic agents [10], anticoagulant [11], anti-inflammatory agents [12], antibiotics [4], and the mechanical factors of intestinal segregation [13].

On the other hand, recent studies have been performed on the anti-adhesion effects via various drugs for preventing post-operative peritoneal adhesion. For example, in a study by Schuinski et al. [14] reported that this medicament did not reduce peritoneal adhesion in rat.

Also, in a study done by Du et al. in 2015 to investigate the effect of sodium carboxymethyl cellulose and dexamethasone on peritoneal adhesion in the rat, it was observed that carboxymethyl cellulose and dexamethasone could prevent peritoneal adhesion. It can also prevent the migration of inflammatory cells. It also plays an important role in reducing fibrosis and proliferation on the serous layer [15].

However, none of these methods is still effective in preventing adhesion, and the incidence of postoperative abdominal adhesion is still high.

Clobetasol is a corticosteroid combination and a potent anti-inflammatory drug that is currently used to treat severe inflammatory diseases and to eliminate surgical scars. In the early inflammation phase after the peritoneal trauma, this compound can reduce secretions, oedema, infiltration of leukocytes and inflammation, and intensify the repair process in the late phase by increasing the angiogenesis. Due to this mechanism, it probably prevents the mechanism of adhesion and post-operative adhesion formation. Considering the high incidence of adhesion after surgery, the numerous complications of adhesions (including obstruction, peritonitis, prolonged anesthesia and possible subsequent surgeries, increased likelihood of complications in subsequent surgeries, increased costs, increased hospitalization time etc.) and lack of knowledge of appropriate ways for reduction of adhesions, in this research we

embarked upon investigating the effect of clobetasol solution on the level of adhesion after laparotomic surgery in rats.

2. MATERIALS AND METHODS

This study was done experimentally (invivo). The study population was albino male rats with the weight between 250-300 g and the age of 8-12 weeks. Considering that no study has been done with this goal, this study was performed on 5 groups of 10 rats.

Inclusion criteria:

- Male Rat
- Albino breed
- Weight between 250-300 g
- Age of 8-12 weeks

Exclusion criteria:

- Rats who die during the study were excluded from the study.

After anaesthesia with 50 mg/kg ketamine hydrochloride as their dorsal surface was placed on the surgery table and after incision that the animal's stomach hair was erased with a razor blade, the laparotomy midline cutting with the length of 5 cm was done on the animal abdomen. The cecum was exposed, and with 10 blow of dry sterile gauze on the cecum, the hemorrhagic surface was created on the cecum with a length of 5 cm. Animals were divided into 5 groups (each group of 10 mouse rats). In groups of 1-3, 5 cc per rat of clobetasol solution in concentrations of 0.05, 0.025 and 0.0125 percent and in group 4, 5 cc of clobetasol solvent (paraffin) were poured in the surface lesion and RLQ of rat's abdomen. In group 5 (no intervention or control group), no substance was poured. Afterwards, an incision was closed and the cecum was returned to the abdomen, and the midline cutting was sewn in two layers with vicryl -5 and nylon 0-5 sutures.

To assess adhesion, 14 days after surgery, and all rats were again subjected to laparotomy. To study adhesion, a scoring system that includes variables of adhesion rate and severity was used.

Adhesion, a percentage of surface affected by adhesion, or the number of bands formed, is as described in the following:

- Score 0: no adhesion
- Score 1: involvement of 1-25% or a band
- Score 2: Involvement of 25-50% or 2 bands
- Score 3: Involvement of 51-75% or more than 2 bands
- Score 4: Involvement of 76-100% or complete adhesion

The grading of adhesion severity was determined as follows:

- Score 0: without adhesion
- Score 1: Adhesive bands that are easily separable.
- Score 2: releasing adhesion requires a gentle, delicate, unobtrusive manipulation.
- Score 3: An agile manipulation is required to release adhesion.

For pathological examination of adhesion, 2 cm of cecum were manipulated, resected and fixed in formalin and sent to the pathology department of Hospital. From each sent sample, two stains were prepared by a pathologist. A stain with H & E and another stain was coloured with trichrome. In the H & E stains, we examined vascular proliferation, inflammation, the formation of granulation tissue, serous layer restorations and fibrosis. The H & E stain results were divided into 3 groups:

- The first group (Score 0): A complete serous layer without granulation tissue, with no fibrosis of inflammatory cells, is seldom.
- Second Group (Score 1): Vascular proliferation with moderate fibrosis and inflammation.
- Third Group (Score 2): Extensive fibrosis and inflammation with the dominant proliferation of vessels is without restoration.

In the trichrome stains, the extent of fibrosis was examined and the results were determined in 4 groups:

- First group (Score 0): lack of fibrosis
- Second Group (Score 1): Fibrosis is less than 30%.
- Third group (Score 2): Fibrosis is 30-70%.
- Fourth Group (Score 3): Fibrosis is more than 70%.

Then, in each group of rats under study, the frequency of rate and severity of adhesion, as well as the frequency of proliferation and inflammation and the extent of fibrosis were

calculated separately and compared with each other.

2.1 Data Analyze

The data were analysed by SPSS23 software. For studying the difference in the frequency distribution of the rate and intensity of adhesion, as well as the amount of proliferation and inflammation, and the extent of fibrosis, Chi-square test or Fisher's exact test were done in each group. The Kolmogorov-Smirnov test was used to examine the normality of the data. The significance level was considered below 0.05.

3. RESULTS

Of the 50 rats, 3 rats died without any determinate reason, one rat died on the third day and two ones on the fifth day. The results of the frequency distribution of adhesion rate in the groups under study have been presented in Table 1. As can be seen, there is no significant difference in the frequency distribution of adhesion between the 5 groups (p = 0.128).

The results of the frequency distribution of adhesion severity in the groups under study are given in Table 2. As can be seen, there is a significant difference in the frequency distribution of adhesion severity among the 5 groups. Among the groups, the group of Clobetasol 0.025% was more effective in reducing adhesion severity than other groups (p = 0.018).

The results of the frequency distribution of inflammation in the groups under study have been given in Table 3. As can be seen, the frequency distribution of inflammation is not significantly different among the 5 groups (p = 0.063).

The results of the frequency distribution of the extent of fibrosis in the groups under study have been given in Table 4. As can be seen, the frequency distribution of the extent of fibrosis is not significantly different among the 5 groups (p = 0.068).

The results of the frequency distribution of adhesion in the clobetasol (integrated) groups and control and paraffin groups have been given in Table 5. As can be seen, there is a significant difference in the frequency distribution of adhesion between the 3 groups; it indicates that the rate of adhesion in the clobetasol groups was lower than the control and paraffin groups (p = 0.028).

Table 1. The frequency distribution of the adhesion rate according to the groups under study

Rate of adhesion	Control group	Paraffin group	Group of clobetasol 0.05%	Group of clobetasol 0.025%	Group of clobetasol 0.0125%	P value *
Without adhesion	0 (%0)	0 (%0)	1 (%1.11)	1 (%10)	0 (%0)	
%1-26	0 (%0)	2 (%2.22)	4 (%4.44)	4 (%40)	1 (%10)	
%26-50	3 (%3.33)	2 (%2.22)	3 (%4.33)	3 (%30)	6 (%60)	0.128
%50-75	5 (%6.55)	2 (%2.22)	1 (%1.11)	2 (%20)	3 (%30)	
%75-100	1 (%1.11)	3 (%3.33)	0 (%0)	0 (%0)	0 (%0)	
Total number	9 (%100)	9 (%100)	9 (%100)	10 (%100)	10 (%100)	

Fisher's exact test

Table 2. Frequency distribution of adhesion severity regarding groups under study

Severity of adhesion	Control group	Paraffin group	Group of clobetasol 0.05%	Group of clobetasol 0.025%	Group of clobetasol 0.0125%	P value *
Without adhesion	0 (%0)	0 (%0)	0 (%0)	1 (%10)	0 (%0)	
Easy separability of the adhesive band	0 (%0)	0 (%0)	0 (%0)	5 (%50)	1 (%10)	
Adhesive band separated by non-agile manipulation	4 (%44.4)	5 (%55.6)	5 (%55.6)	3 (%30)	7 (%70)	0.018
Adhesive band separated by agile manipulation	5 (%55.6)	4 (%44.4)	4 (%44.4)	1 (%10)	2 (%20)	
Total number	9 (%100)	9 (%100)	9 (%100)	10 (%100)	10 (%100)	

Fisher's exact test

Table 3. Frequency distribution of inflammation rate regarding groups under study

Rate of inflammation	Control group	Paraffin group	Group of clobetasol 0.05%	Group of clobetasol 0.025%	Group of clobetasol 0.0125%	P value *
Without inflammation	0 (%0)	0 (%0)	2 (%22.2)	1 (%10)	0 (%0)	
Moderate inflammation	0 (%22.5)	1 (%11.1)	3 (%33.3)	4 (%40)	4 (%40)	0.063
Intense inflammation	9 (%100)	8 (%88.9)	4 (%44.5)	5 (%50)	6 (%60)	
Total number	9 (%100)	9 (%100)	9 (%100)	10 (%100)	10 (%100)	

Fisher's exact test

Table 4. Frequency distribution of extent of fibrosis regarding groups under study

Extent of fibrosis	Control group	Paraffin group	Group of clobetasol 0.05%	Group of clobetasol 0.025%	Group of clobetasol 0.0125%	P value *
Without fibrosis	1 (%11.1)	2 (%22.2)	5 (%55.5)	4 (%40)	4 (%40)	
Lower than 30%	5 (%55.6)	3 (%33.3)	4 (%44.5)	6 (%60)	6 (%60)	0.068
%30-70	3 (%33.3)	4 (%44.4)	0 (%0)	0 (%0)	0 (%0)	
%70-100	0 (%0)	0 (%0)	0 (%0)	0 (%0)	0 (%0)	
total number	9 (%100)	9 (%100)	9 (%100)	10 (%100)	10 (%100)	

Fisher's exact test

Table 5. Frequency distribution of adhesion rate regarding groups under study (with the integration of clobetasol groups)

Rate of adhesion	Control group	Paraffin group	Clobetasol groups	P value *
Without adhesion	0 (%0)	0 (%0)	2 (%6/9)	
%1-26	0 (%0)	2 (%22.2)	9 (%31)	
%26-50	3 (%33.3)	2 (%22.2)	12 (%41.4)	0.028
%50-75	5 (%55.6)	2 (%22.2)	6 (%20.7)	
%75-100	1 (%11.1)	3 (%33.3)	0 (%0)	
Total number	9 (%100)	9 (%100)	29 (%100)	

Fisher's exact test

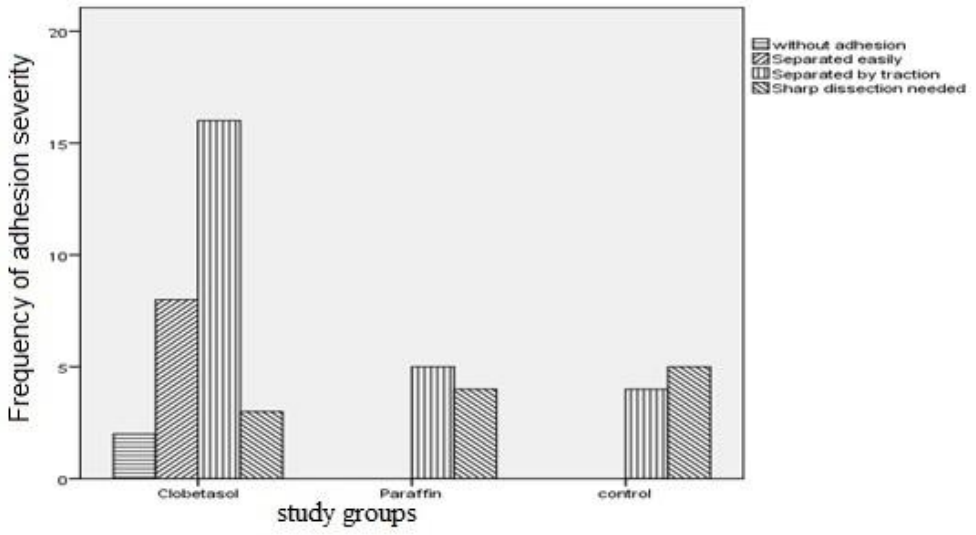

Fig. 1. Frequency distribution diagram for adhesion severity in the groups under study along with the integration of the clobetasol groups

The results of the frequency distribution of adhesion severity among the clobetasol (integrated) groups and control and paraffin groups have been given in Fig. 1. As can be seen, there is a significant difference in the frequency distribution of adhesion severity between the 3 groups; it indicates that the severity of adhesion in the clobetasol groups was lower than the control and paraffin groups (p = 0.03).

The results of the frequency distribution of inflammation among the (integrated) clobetasol groups and the control and paraffin groups have been given in Fig. 2. As it can be seen, the frequency distribution of inflammation among the 3 groups has a significant difference (p = 0.048).

The results of the frequency distribution of the extent of fibrosis among the (integrated) clobetasol groups and control and paraffin groups have been given in Fig. 3. As can be seen, there is a significant difference in the frequency distribution of the extent of fibrosis between the 3 groups; it indicates that the extent of fibrosis in the clobetasol groups was lower than the control and paraffin groups (p = 0.02).

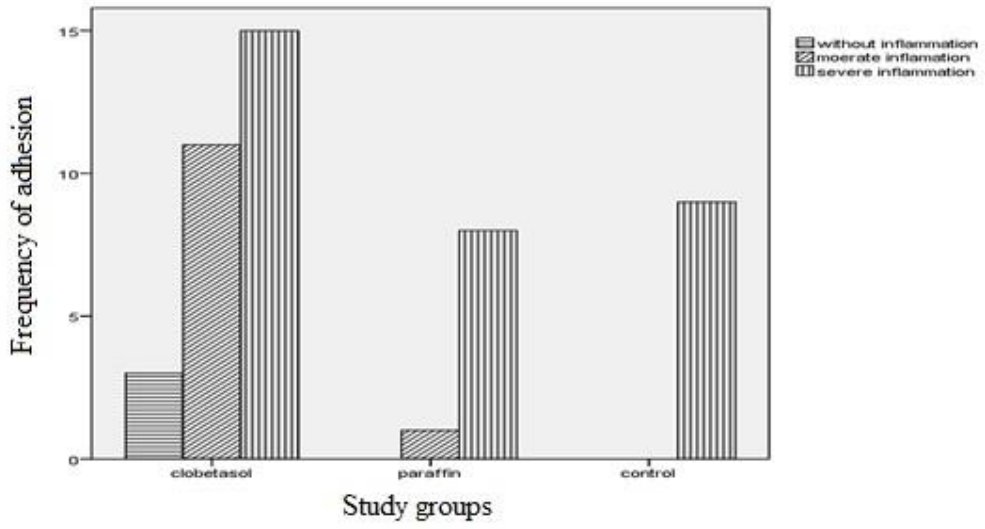

Fig. 2. Frequency distribution diagram for inflammation in the groups under study along with the integration of the clobetasol groups

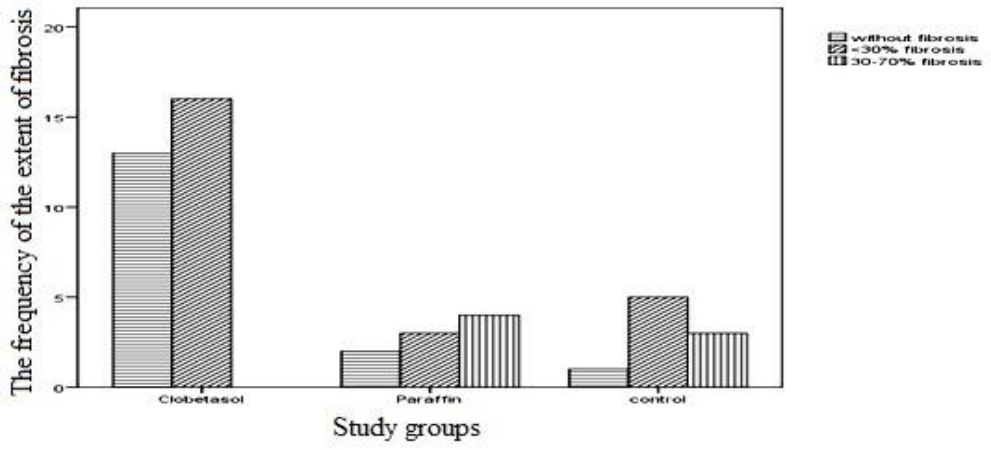

Fig. 3. Frequency distribution of the extent of fibrosis among the (integrated) clobetasol groups and control and paraffin groups

3.1 Histopathological Results

In the H & E staining of control group samples, the non-repair of mesothelial cells was observed in serous layers. The proliferation of capillary vessels and fibroblastic cells accompanied by intense and extensive infiltration of acute and chronic inflammatory cells, including neutrophils, lymphocytes, plasma cells, and hystiocytic cells were evident (Figs. 4 and 5).

Compared to the control group, modest histologic changes were observed in the groups receiving clobetasol. At serous layer, a partial repair of mesothelial cells was evident. The proliferation of fibroblastic and capillary cells accompanied by infiltration of inflammatory cells was observed in less extent and severity than the control group (Fig. 6).

In the trichrome staining of the control group samples, the connective-adipose tissue of serous layer was in a large extent replaced by the thick and compressed collagen bands (Fig. 7).

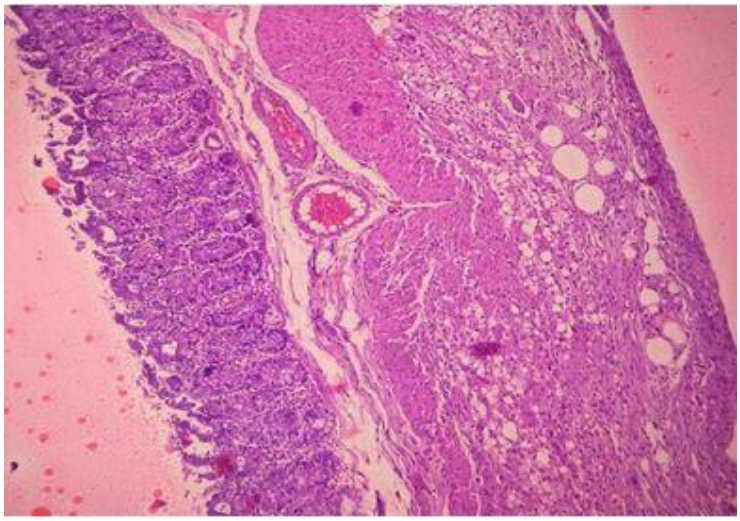

Fig. 4. Serous H & E staining in rats of the control group with high inflammation

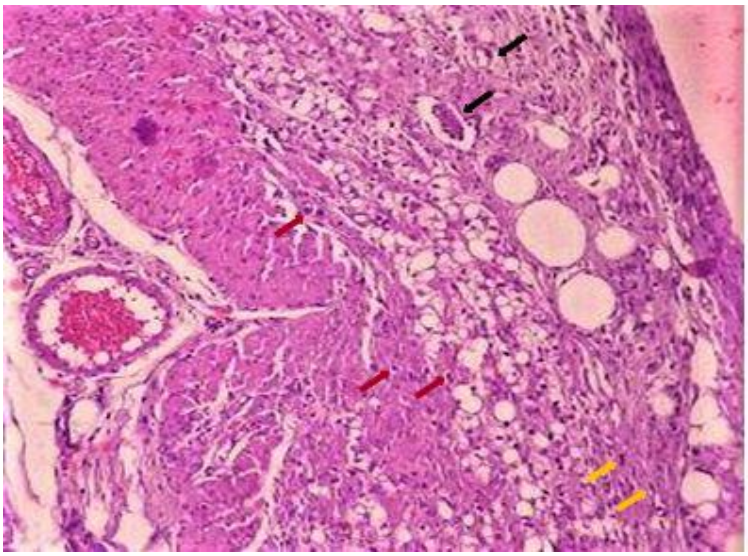

Fig. 5. Serous H & E staining with magnification in rats of the control group with high inflammation. Capillary vessels proliferation (black arrow), the proliferation of fibroblasts (yellow arrow) and infiltration of lymphocytes (red arrow)

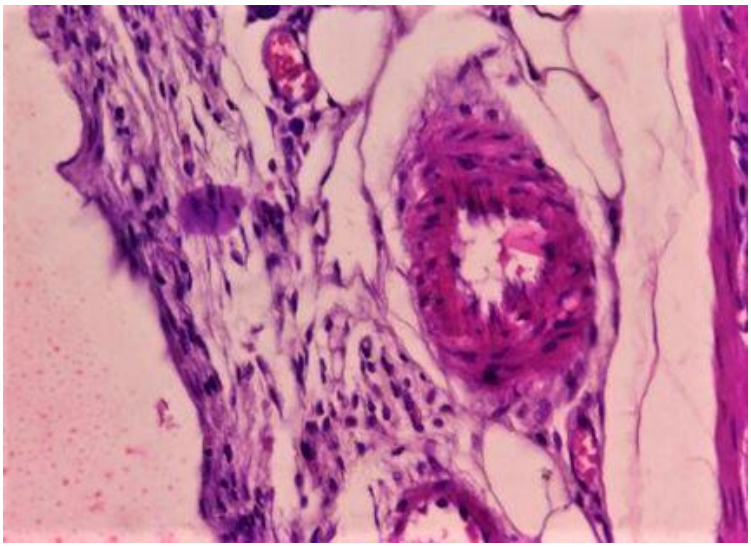

Fig. 6. Serous H & E staining in rats of clobetasol 0.05% group with low inflammation

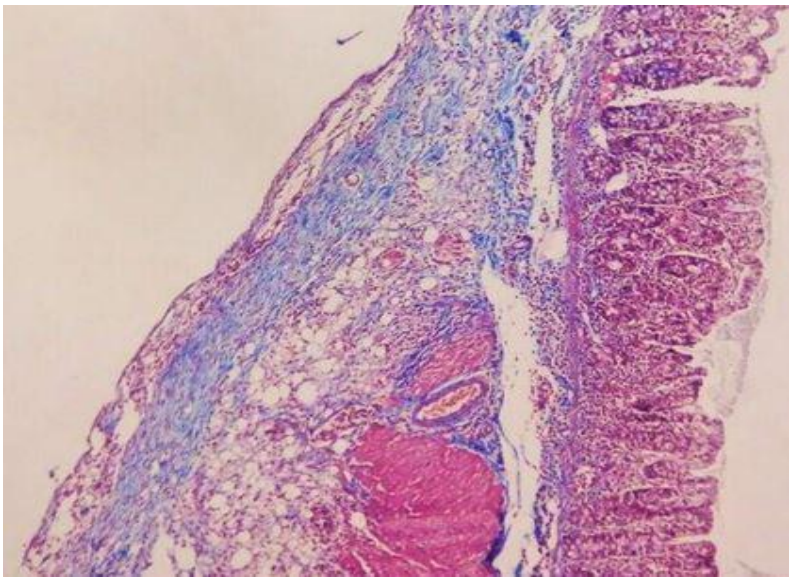

Fig. 7. Serous Trichrome Staining in rats of Control group with High Fibrosis. Thick collagen bands are seen to be blue

Compared to the control group, by the groups receiving clobetasol, a milder fibrosis in the form of the subtle and scattered collagen bands was evident in the connective-adipose tissue of serous layer (Fig. 8).

4. DISCUSSION

Nowadays, many cases of surgery on the abdomen and pelvis occur for various reasons such as appendicitis, stone and gallbladder inflammation, diagnostic laparotomy, abdominal and pelvic tumours removal, peritonitis treatment, intestinal obstruction, trauma, restoration of abdominal entrails tear, etc. Peritoneal adhesion is one of the common side effects of these surgeries. After surgery, a layer of fibrin membrane covers all surfaces of the abdomen, which is exacerbated by an external object (sterilised gas, talcum powder, gloves, residual suture etc.) and ischemia. For unknown reasons, plasminogen secretion may be inhibited, and fibrin fibres remain undamaged. Failure to secrete tissue plasminogen and the remaining of

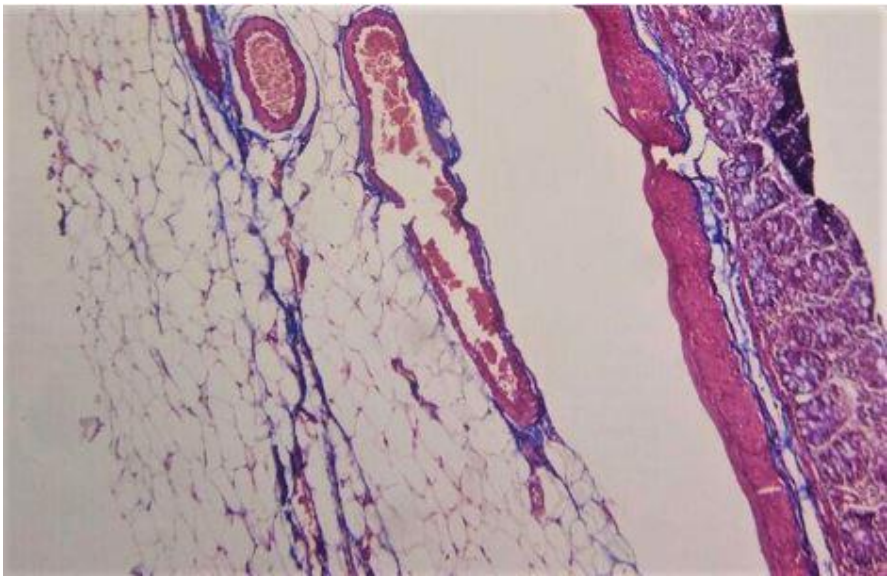

Fig. 8. Serous Trichrome Staining in rats of clobetasol 0.05% group with Low Fibrosis. Subtle collagen bands are seen to be blue

the fibrin layer cause fibroblasts to migrate to the place and the fibrous tissues that result in adhesion of the adjacent elements are formed. Adhesion formation has significant side effects and occurs after abdominal surgery, especially after extensive surgery, pelvic surgery, or multiple abdominal surgeries. Naturally, no automatic adhesion is probably due to inflammation of the cases of the autopsy. The rate of intra-abdominal adhesion formation was 70-90% in clinical and autopsy studies in patients undergoing laparotomy [4].

This study aimed to evaluate the topical effect of clobetasol solution in different doses on the amount and severity of adhesion, as well as the rate of inflammation and the extent of fibrosis on peritoneum following laparotomic surgery on day 14 in rats. There was no significant difference in the frequency distribution of adhesion between the 5 groups ($p = 0.128$), but we observed a significant difference in the frequency distribution of adhesion severity among the 5 groups; among the groups, the group of clobetasol 0.025% was more effective regarding the reduction of adhesion severity ($p = 0.018$). Regarding the frequency distribution of inflammation and the extent of fibrosis, there was no significant difference between the 5 groups ($p = 0.063$ and $p = 0.068$, respectively). In the case of integrating of the clobetasol groups in a group and comparing it with the control and paraffin groups, there occur a significant difference in the amount and severity of adhesion, as well as the rate of inflammation and extent of fibrosis among the three groups ($p = 0.028$, $p = 0.03$, $p = 0.002$, $p = 00.48$). Due to the correspondence of macroscopic observations during surgery respecting the severity and rate of adhesion and histopathologic findings in the field of fibrosis and inflammatory infiltration, it seems that clobetasol reduces adhesion by reducing the inflammation.

In the study of Soltani et al. [16], it was shown that the washing of rats' peritoneum with dexamethasone does not affect the amount and severity of intraperitoneal adhesion; it contradicts our study result. In our study, clobetasol, by reducing inflammation, reduced the amount and severity of adhesion and the extent of fibrosis. Çubukçu et al. have suggested that, considering the available mechanism, inhibiting inflammatory cells by drugs such as dexamethasone, as well as inhibiting fibroblasts with anti-fibrotic mitomycin drug, can stop the formation of adhesion bands [17]. In another study conducted by Gazzaniga AB et al. the authors have concluded that intraperitoneal use of dexamethasone in rats reduces adhesion but does not affect its severity [18]. But in our study, both the rat of adhesion and the severity of adhesion decreased. It has been shown, in a study by Kirdak et al. that various doses of methyl prednisolone topically are of no effect on the rat's peritoneum, contrary to the results of our study, in preventing adhesion and peritoneum

fibrosis [19]. In other studies, various drugs have been used to prevent and reduce postoperative adhesion. In the study conducted by Risberg et al., it has been found that many chemicals inhibit proliferation of fibroblasts and reduce peritoneal fibrosis; they comprehend NSAIDs, corticosteroids, and calcium channel blockers, histamine antagonists, antibiotics, fibrinolysin, Anticoagulants, antioxidants, hormones, vitamins, colchicine and immunosuppressants [20].

On the other hand, in a study on patients with gastric cancer for intraperitoneal chemotherapy, Adachi et al. used the combination of mitomycin and Cis-diamminedichloroplatinum before surgery and observed that in 25% of patients, large adhesive bands were created; it had no significant effect in the prevention of sticky bands [21]. In the study of Menzies et al., as in our study, it has been shown that in some animal models the NSAIDs have reduced peritoneal adhesion by inhibiting the synthesis of prostaglandins and thromboxane [22]. In a study conducted by Guvenal et al. it is shown that the preoperative intramuscular injection and the postoperative intraperitoneal injection of nimesulide reduce adhesion of the peritoneum after surgery [23]. In the study of Nappi et al. it has been stated that generally speaking, some anti-inflammatory drugs inhibit peritoneal adhesion, but no study provides evidence for their use in humans for such a purpose [24]. In parallel, Wei et al. [25] suggested that intraabdominal adhesions are a very common complication following abdominal surgery.

5. CONCLUSION

It seems that the local solution of clobetasol with its anti-inflammatory property as well as accelerating the repair process can play a key role in preventing the incidence, severity and complications of adhesion after laparotomic surgery. But with an animal study, this strategy cannot be recommended for use in the operating room, and to prove these more studies are necessary.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard was written ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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