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EFFICACY OF VIRGIN OLIVE OIL IN PREVENTING POSTOPERATIVE PERITONEAL ADHESIONS

Fatih YURDADOGAN[1], Hatice Sonay YALCIN COMERT[2]*, Ismail SAYGIN[3], Haluk SARIHAN[2]

[1]*Department of Pediatric Surgery, Kanuni Education and Research Hospital, 61080, Trabzon, Turkey*
[2]*Department of Pediatric Surgery, Karadeniz Technical University Faculty of Medicine, 61080, Trabzon, Turkey*
[3]*Department of Pathology, Karadeniz Technical University Faculty of Medicine, 61080, Trabzon, Turkey*

Abstract: Postoperative peritoneal adhesions (PPA) can be formed by any damage to mesothelial cells of peritoneum. Many methods were used to prevent the formation of PPA. Our purpose is to appraise the efficiency of virgin olive oil on PPA before and after formed traumatic peritoneal adhesions. A total of thirty-two rats were divided into four equal groups. Group1 (sham group): Virgin olive oil was applied intraperitoneally. Group2 (control group): Adhesion model was created. Group3: After the adhesion model was created, virgin olive oil was applied to the caecum. Group4: After applying caecum with virgin olive oil, the adhesion model was created. The experiment ended on day 10. Macroscopic and histopathological assessments were made. Compared with Group2 there was a statistically significant reduction in PPA in Group 3 and Group4 results ($P < 0.001$). Any statistically significant difference was found between Group 3 and Group4 ($P > 0.05$). Considering our results, we believe that virgin olive oil can reduce the formation of PPA when it has been applied before or after surgical trauma by its anti-inflammation and hydroflotation effects.

Keywords: Adhesions, Virgin olive oil, Peritoneum

***Corresponding author:** Department of Pediatric Surgery, Karadeniz Technical University Faculty of Medicine, 61080, Trabzon, Turkey
E mail: sonayyalcin@hotmail.com (H.S. YALÇIN COMERT)

Fatih YURDADOGAN https://orcid.org/0000-0002-5288-0199
Hatice Sonay YALCIN COMERT https://orcid.org/0000-0002-5281-4933
Ismail SAYGIN https://orcid.org/0000-0002-6013-6378
Haluk SARIHAN https://orcid.org/0000-0002-0991-8235

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1. Introduction

Peritoneal adhesions; pathological fibrotic bands formed between the surfaces in the peritoneal space (Tittel et al., 2001). Adhesions are usually due to surgical intervention but are also observed in peritonitis, endometriosis, pelvic inflammatory disease, long-term peritoneal dialysis, chemical peritonitis, radiotherapy, and cancer (Holmdahl and Risberg, 1997).

Although advances in surgery and technology have increased our knowledge of postoperative peritoneal adhesions (PPA), PPA continues to be a problem for surgeons from different disciplines. Advances in anesthesia and surgery have led to an increased number of laparotomies which lead to an increase in PPA (Risberg et al., 1997).

PPA eventuate in more than 90% of all laparotomies, most of them are silent but 3% cause intestinal obstruction. PPA leads to postoperative morbidity, mortality, and cost increase due to the need for secondary surgery and prolongation of hospitalization. Also, the most general reason for female infertility in developed countries is PPA (Holmdahl and Risberg, 1997; Risberg et al., 1997).

Due to its barrier-forming properties that reduce fibroblastic activity and lubricity to prevent PPA; soybean oil, aloevera gel, honey, vitamin E, canolaoiltried many different substances such as tried but not enough therapeutic results.

Olive oil has become the focus of interest in medicine due to the various effects of the phenolic components it contains. Phenolic components have antiatherogenic, antioxidant, anticancer, anti-inflammatory, skin-protective, and endothelial function-improving properties (Tranter et al. 1993; de la Puerta et al., 2000; Tuck and Hayball, 2002; Tripoli et al., 2005). Also, olive oil has interfacial lubricant and mechanical barrier properties.

We planned this experimental study, to investigate the efficacy of virgin olive oil in preventing PPA. If we achieve success in our experimental study, we think that virgin olive oil can be cheap, easy to obtain, and can be applied to the clinic.

2. Material and Methods

This experimental study was planned by Karadeniz Technical University, Faculty of Medicine Department of Pediatric Surgery with the contributions of Pathology and Anesthesia and Reanimation Departments. The rats used in the study were provided from the Experimental Animal Research Center of Karadeniz Technical University. 32 female rats weighing 250-300 g were housed under the same conditions. Animals were divided

into four equal groups. Anesthesia was achieved with intramuscular75mg / kg ketamine and 10mg / kg xylazine.

Group-1 (sham group): Virgin olive oil was applied intraperitoneally by 22 french diameter needle.

Group-2 (control group): Adhesion model was created.

Group-3: After the adhesion model was created, virgin olive oil was applied to the caecum.

Group-4: After applying caecum with virgin olive oil, the adhesion model was created.

2.1. Adhesion Model

The experimental adhesion model that we used in our study was provided with the device especially designed for this work (Figure 1). The arrangement consists of a wooden operating table with a size of 2x1 cm and a three-piece (two fixed, one moving) arm that is wooden. Owing to the mechanism, the movable arm can freely move the pendulum in the air. In this way, the lower end of this arm in contact with the subject can make abrasion by contacting an area of 2 cm^2. On the end of the wooden rod contacting the peritoneal surface, a sterile surgeon gloved a gloved finger to simulate both Standard human hand fingers and sterilization. Thus, a standard trauma may be formed on a selected peritoneal surface, weight, surface area, and number. In our study, we used a weight of 0.5 kg and applied the pendulummotion to the front of the cecum 10 times.

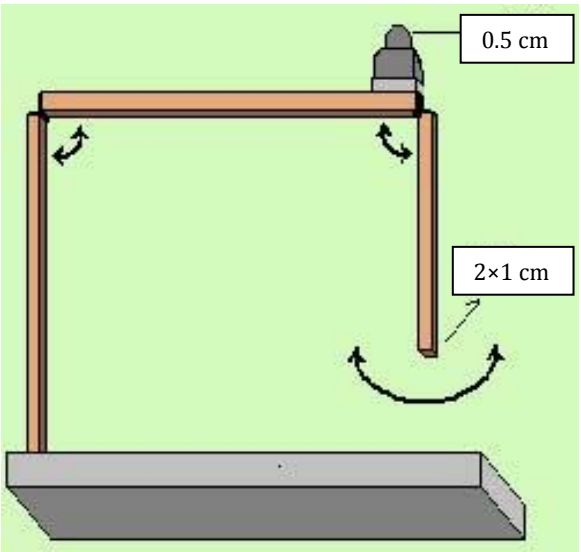

Figure 1. The standard experimental adhesion model forming device.

2.2. Obtaining and Sterilizing Virgin Olive Oil

Virgin olive oil made by cold press extraction method from Mustafa Kemal University Agricultural Engineering in Antakya. The sterilization of olive oil was achieved by filtering the sterile centrifuge tube from a 0.45 nm porefilter. The pH value of virgin olive oil was 6.8 and as same as the pH of peritoneal dialysis liquid.

2.3. Study Design

The rats fasted for 12 hours before the operation and the appropriate anesthesia was given and the abdominal anterior wall of the rats in Group1 was injected peritoneally into the peritoneal cavity with a standard plastic inject or needle of 22 french diameter and 1 ml of sterile virgin olive oil was injected. After 12 hours postoperatively, the rats were fed with their usual feed. On the10th postoperative day, these rats were sacrificed. Laparotomy was performed with reverse U-incision. A 2 cm^2 area was removed from the anterior surfaces of the cecum without damaging the adhesions andvials containing formol were placed for histopathological examination.

After appropriate anesthesia, rats in Group 2 were placed on the surface of the device, which was designed as an operating table, to create an experimental adhesion model. The midline of the abdomen where the incision was to be applied was shaved, and the cut hairs were completely removed from the area and sterility was maintained with the povidone-iodine solution (Betadine®, Kurtsan Co). The laparotomy was done with a three-centimeter vertical midline incision. The caecum was carefully taken out of the abdomen by a caudally held wetsponge. The surgeon's left hand was placed on these condfinger and the adhesion device was placed under the 2 × 1 cm surface of the pendulummotion and an adhesion model was created. The reason why the adhesion model was applied to the cecum is that the PPA in the clinic is most commonly seen in this region after appendectomies. Then the cecum was thrown into the abdomen. The incision was closed with 3/0 propylene (Dogsan) continuous suture technique. After 12 hours postoperatively, the rats were fed with their usual feed and treated in Group 1 postoperatively on the10th postoperative day.

Group 3 rats were applied adhesion model like Group 2 rats and then 1 ml sterile virgin olive oil was sprayed to this area and then the peritoneal cavity was closed with the same technique. Postoperative procedures were performed as in Group 1.

After anesthesia and laparotomy for the rats in Group 4, 1ml of sterile virgin olive oil was sprayed to the cecum on which the adhesion model would be created. Then the adhesion model was performed. The incision was discarded and the incision was closed. Sacrification and subsequent procedures were performed as in Group 1.

2.4. Adhesion Assessment

Adhesion was evaluated in two ways as macroscopic and microscopic. Macroscopic adhesion assessment: Evans' adhesion scoring was used Cömert et al., (2010). Evans' adhesion; it has been classified in two ways according to the adhesion strength and adhesion field. Microscopic adhesion evaluation: 2 cm^2 cecum frontal wall and all adhesions on this surface were fixed in formol. It was sunk in parafin after dehydration. 5 mm sections were acquired and stained with hematoxylin-eosin and evaluated by a pathologist who was unaware of which group the preparations belonged to. All histopathological evaluations were performed at x100 magnification with a light microscope. The histopathological rating was based

on Zühlke's classification (Broek et al., 2018).

2.5. Statistical Analysis

The data were evaluated using SPSS 13.01 statistical program package. In this study, descriptive statistical methods (mean, standard deviation, median) as well as Kruskal Wallis test were used for comparison between groups, and Mann Whitney U test with Bonferroni correction was used for subgroup comparison (Onder, 2018). Our outcomes were judged at a 95% assurance interval and $P < 0.05$.

2.6. Ethical Consideration

The ethical approval was taken from the Presidency of Ethics Committee of Karadeniz Technical University, Medical Faculty numbered: 2013-13.

3. Results

When the groups were examined macroscopically and morphologically, rats from Group 1 were excluded from the evaluation because no adhesion was detected (only olive oil is injected intraperitoneally).

In the statistical evaluation of the adhesion strength of the groups; in comparison to Group 3 and Group 4 with Group 2 separately, Group 3 and Group4's adhesion strengths cores were statistically significantly lower than Group 2 ($P < 0.001$). No statistically significant difference was found between Group 3 and Group 4 in terms of adhesion strength scores (Table1).

Table 1. Adhesion strength and adhesion area scores of groups

Groups	Evan's adhesion strength scores				Total	Evan's adhesion area scores			Total
	0	1	2	3		0	1	2	
Group 2	0 (0%)	2 (25%)	5 (62.5%)	1 (12.5%)	8 (100%)	0 (0%)	2 (25.0%)	6 (75.0%)	8 (100%)
Group 3	6 (75%)	2 (25%)	0 (0%)	0 (0%)	8 (100%)	6 (75.0%)	2 (25.0%)	0 (0%)	8 (100%)
Group 4	7 (87.5%)	1 (12.5%)	0 (0%)	0 (0%)	8 (100%)	7 (87.5%)	1 (12.5%)	0 (0%)	8 (100%)
Total	13 (54.2%)	5 (20.8%)	5 (20.8%)	1 (4.2%)	24 (100%)	13 (54.2%)	5 (20.8%)	6 (25.0%)	24 (100%)

Group 3 and 4's adhesion strength scores were statistically significantly lower than Group 2 ($P < 0.001$). No statistically significantly difference was found between the Group 3 and 4 ($P > 0.05$) with Man Whitney U test. Group-3 and Group-4 adhesion field scores were significantly lower than Group-2 ($P < 0.001$). No statistically significant difference between the Group 3 and Group 4 ($P > 0.05$) with Man Whitney U test.

When groups are evaluated according to Evans' adhesion areas coring; in two of the rats in Group 2 (25%), the score was one and six (75%) were two. Six (75%) of the patients in Group 3 had zero and two (25%) had one.

Seven (87.5%) of the rats in Group 4 had a score of zero and one (12.5%) had one. Group-3 and Group-4 scores were significantly lower than Group-2 ($P < 0.001$). When we compared Group-3 and Group-4, there was no statistically significant difference in terms of adhesion field score (Table1).

According to the microscopic adhesion score classification, two of the rats in Group 2 (25%) were Grade three changings and six (75%) were Grade four changings (Figure 2a, b).

Five (62.5%) of the rats in Group 3 had Grade one changing and three (37.5%) had Grade two changes. Six (75%) of the rats in Group 4 had grade one changing and two (25%) had Grade two changes. In the comparison of Group 3 and Group 4 with Group 2, Group 3 and 4 microscopic adhesion scores were significantly lower than Group 2 ($P < 0.001$). There was no statistically significant difference in terms of microscopic adhesion score in Group 3 compared with Group 4. All the microscopic results were summarized in Table 2.

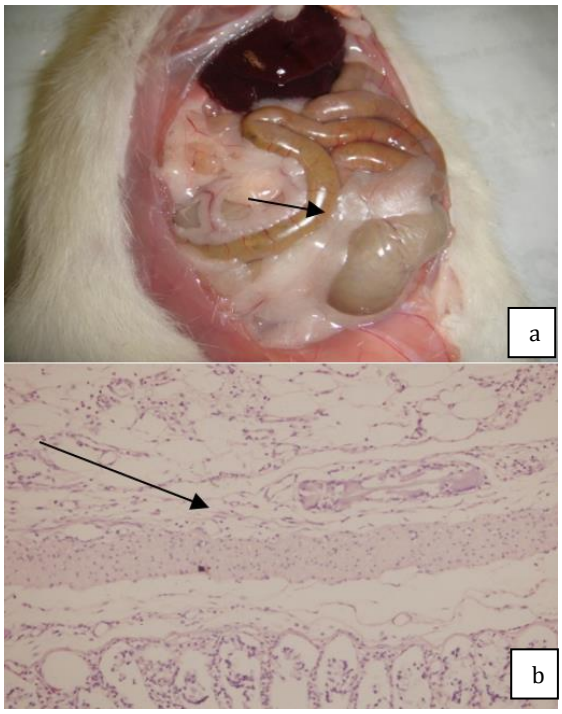

Figure 2. a) Advanced adhesions in the abdomen and related ileus showned with arrow. b) Old thick granulation tissue, rare cells, diffucult seperation of serosal layers (Grade 4).

Table 2. Histopathological microscopic adhesion scores

Groups	Microscopic adhesion scores				Total
	Grade 1	Grade 2	Grade 3	Grade 4	
Group 2	0(0%)	0(0%)	2 (25%)	6(75%)	8
Group 3	5(62.5%)	3(37.5%)	0(0%)	0(0%)	8
Group 4	6(75%)	2(25%)	0(0%)	0(0%)	8
Total	11(45.8%)	5(20.8%)	2(8.3%)	6(25%)	24

Group 3 and 4 microscopic adhesion scores were significantly lower than Group 2 ($P < 0.001$). No statistically significant difference between Group 3 and Group 4 ($P > 0.05$).

4. Discussion

Adhesion development is a kind of normal peritoneal healing process. Traumatic factors such as mechanic, chemical, thermal, foreign body, and inflammatory damage, the unaffected peritoneum initiates a series of events leading to the adhesion (Tranter et al., 1993; Risberg et al., 1997). Damage to the peritoneal mesothelial cell surface makes the connective tissue in contact with the peritoneal fluid. This results in increased levels of leukotriene B4 and prostaglandin E2 (PGE2) in the peritoneal fluid and inhibition of plasminogen activator activity (PAA) (Heinonen et al., 1990). While leukotriene B4 and PGE2 increase stimulate adhesion, PAA inhibition reduces fibrin degradation and consequently changes in favor of equilibrium adhesion formation.

There are two main processes for the prevention of PPA. The first is the prevention of peritoneal trauma and the other is the prevention of adhesion of the peritoneal area to any surface.

To prevent trauma, careful, less traumatic surgical techniques should be applied. In our opinion, intervening in the first stage is a much simpler and more efficient method. It is because it is necessary to create a barrier to prevent trauma. It is efficient because; the inflammation and wound healing processes that begin after the trauma are rather complicated and involve many unknown steps. The chances of success in applications to be performed without clarifying the physiopathology of these processes will be lower. Moreover, whatever the substance/method to use after trauma occurs; on the one hand it must not have toxic outcomes on peritoneal mesothelial cells, but also, it must force wound healing and/or prevent the adhesion of mesothelial surfaces to each other until this process is completed.

After the formation of peritoneal trauma, various fluids and gels were used to prevent the formation of PPA, which could form a mechanical barrier between fibrin formation and inflammation-inhibiting agents and mesothelial surfaces. Although useful techniques or factors have been found, no full effectiveness has been achieved (Menzies and Ellis, 1990; Maciver et al. 2011).

To prevent fibrin deposition, anticoagulant agents include heparin and enoxaparin; thrombokinase, fibrinolysis, streptokinase, urokinase, hyaluronidase, chymotrypsin, papain, and pepsin have been used in the fibrinolytic agents but there are not enough studies reflected in the clinic (Maciver et al., 2011).

In some stages of inhibition of the cells involved in the inflammatory response and blockage of free oxygen-radical radicals and to prevent fibrinous exudation, agents such as meclofenamate, tolmetin, ibuprofen, nimesulide, oxyphenbutazone, corticosteroid, aspirin, disodiumcromoglycate, Mn-deferoxamine, allopurinol, mannitol, honeyandcatalase (Tranter et al., 1993; Tuck and Hayball, 2002). Muzii et al have shown to be effective in preventing adhesions in their study on rabbits with aspirin (Muzii et al., 1998). Yuzbasioglu et al., (2009) found that adhesions were prevented with honey in their study.

One of the most frequently studied areas in recent years is the mechanical barrier between peritoneal surfaces. For this purpose, substances such as crystalloids, carboxymethylcellulose, hyaluronic acid, glycerol, polytetrafluoroethylene, and seprafilm were used. This treatment method is easy, cheap, and is preferred because of being suitable for peritoneal physiology (Yuzbasioglu et al., 2009).

Gemici et al., (2014) in their study on rabbits with seprafilm showed that the adhesions are highly prevented. Aysan et al., (2010) reported that glycerol is effective in preventing adhesions.

Different models have been improved for experimentally generating PPA. These; abrasion, local peritoneal excision, ischemic injury, foreign body insertion into the peritoneal cavity, thermal damage, and bacterial contamination (Blauer and Collins, 1988).

In this study, we preferred the abrasion model because it mimics the mechanical trauma of the laparotomy. Because all kinds of manipulation by hand or by surgical instruments during laparotomies is a mechanical trauma and is the most common cause of PPA (Drollette and Badawy, 1992; Gomel et al., 1996). In our study, we found that this model we applied in the control group was successful because it caused adhesion in all rats. In our experimental study, there were two reasons why we preferred virgin olive oil to prevent PPAs: firstly, because of the positive effects of virgin olive oil on the wound healing due to its anti-inflammatory and antioxidant effects. The other is that we think that it can prevent PPAs with the effect of hydroflotation because it is a liquid with high viscosity.

In our study, we injected1ml of virgin olive oil into the peritoneal cavity in Group-1 with laparotomy. We aimed

to see the potential effects of virgin olive oil in the peritoneal cavity that was intact (not subjected to any manipulation). In the re-laparotomies performed in this group, we did not see any adhesions macroscopically and morphologically, and we did not find any toxic reaction in the peritoneal cavity. This result suggests that olive oil does not cause any inflammation in the peritoneal cavity. These results show that the application of olive oil after the adhesion model has been formed prevents anti-inflammatory, fibrin-reducing, and hydroflotation adhesions.

5. Conclusion

Our study will shed light on the studies to be carried out in the future and the effects of antiinflammatory substances in virgin olive oil can be purified and individual effects can be investigated. Also, there is a need for further research to prevent the long-term chronic disease of the inflammatory process resulting in adhesion.

Author Contributions

All authors contributed at all stages of the study.

Conflict of Interest

The authors declared that there is no conflict of interest.

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