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Comparison of Intraperitoneal Honey and Dexamethasone for the Prevention of Postoperative Intra-abdominal Adhesions in Rabbit.

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Abstract: The objective of this study was to determine the effectiveness of intraperitoneal administration of honey and dexamethasone in prevention of postoperative intra-abdominal adhesions in rabbit. Material and Methods: 24 rabbits underwent laparotomy.Postoperative intra-abdominal adhesion was induced by scarping serosal the surface of the descending colon and peritoneal layer of the left abdominal wall. The animals were divided into three groups (n=8). Group 1, received normal saline intraperitoneally. Group 2, received honey intraperitoneally.Group 3, received dexamethasone intraperitoneally. After 14 days, the degree of intra-abdominal adhesions was evaluated by using the score method of ultrasonography, traditional dissection and histopathological examination. Results: In ultrasonography and dissection findings, the control group exhibited severe adhesion scores between organs or between organs and abdominal wall.The honey group had fewer adhesive attachments to the intra-abdominal structures.The dexametasone group had moderate adhesion scores between organs.Compared to group 1, the incidence of adhesion formation was lower in both group 2 ($p=0.001$) and group 3 ($p=0.005$).The incidence of fibrosis was also lower in group 2($p=0.001$) and group 3($p=0.002$), compared to group 1. However, there was no significant difference between the fibrosis scores of the 2 and 3 groups ($p=0.069$). Conclusion: This study showed that the intraperitoneal administration of honey and dexamethasone decreased the formation of postoperative intra-abdominal adhesions. However, honey was more effective, and ultrasonography proved to be a useful tool for clinical diagnosis intra-abdominal adhesions.

Key words: Colon abrasion, Dexamethasone, Honey, Postoperative intra-abdominal adhesion Ultrasonography.

INTRODUCTION

Intra-abdominal adhesions may be congenital or acquired, the latter being as a result of a generalised phenomenon in response to trauma to the peritoneum. Postoperative adhesions are almost inevitable after most abdominal and pelvic surgery procedures.The incidence of adhesion formation has been reported to be 93% in patients who have undergone major surgery(Yilmaz *et al*, 2005).Inflammations caused by mechanical or chemical stimuli are the principal common causes of intraperitoneal adhesions (Cox *et al*, 1993 - Rodgers *et al*,1998).In recent years, various methods such as improvements in surgical techniques and instruments,drugs and anti-adhesive barriers have been evaluated to prevent the adhesions. But so far, no ideal method has been found.Intra-abdominal adhesions can induce gastrointestinal obstruction and chronic pain in abdomen and pelvic(Van Der Krabben, 2000). Ultrasonography is a useful tool to diagnose and locate intra-abdominal

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adhesion (Wang *et al*, 2003) .Corticosteroid,one of the most common drugs to reduce inflammation, is used to prevent the formation of abdominal adhesions (Hockel *et al*, 1987- Kucukozkan *et al*, 2004).

Natural honey is a valuable nutrient,Which has been used in healing wounds and burns since ancient times(Mathews, 2002). Physical properties such as hygroscopicity, lower pH and hypertonicity of honey are supposed to be responsible for its wound healing effect (Aysan *et al*, 2002 - Erguder *et al*, 2008). Honey inhibits the growth of both gram-positive and gram-negative bacteria and provides anti-inflammatory, anti-fungal and anti-ulcer effects (Aysan *et al*, 2002 – Yuzbasioglu *et al*, 2009).

The aim of this study was to compare honey with a dexamethasone (Corticosteroid) to prevent the formation of postoperative intra-abdominal adhesions in rabbit.

MATERIALS AND METHODS

This study was performed in accordance with the Islamic Azad University Law on animal experimentation.Rabbits were treated accordingly to animal welfare legal regulations.

Twenty four adult female White New Zealand rabbits with an average weight 2.5-3 Kg were selected. Animals were housed at 22 ºC and given standard rabbit chow diet and water. The animals were not feed for 12 h before operation. All rabbits were anesthetized with a mixture of 35 mg/kg ketamine hydrochloride (ROTEXMEDICA TRITTAU.GERMANY) and 5 mg/kg xylazine hydrochloride (ALFASAN WOERDEN.HOLLAND) intramuscularly. The rabbits were then placed in the supine position and the abdomino-pelvic area was shaved and disinfected for aseptic surgery. A 5cm midline incision was made and the abdomen was opened.Then descending colon was isolated with wet sterile gauze.In order to induce intra-abdominal adhesion, the antimesentric border of the descending colon was scraped with rubbing 100 time dry gauze, until serosal petechiae appeared on the intestinal surface(Moll *et al*, 1991). Then, by blade number 13, ten longitudinal and parallel incisions of 2 -3 cm in length were made on peritoneal layer of left abdominal wall(Avsar *et al*, 2001).

At this stage, the rabbits were randomly divided into three equal groups (n=8).Group 1(control), received a single dose of 5 ml normal saline intraperitoneally. Group 2(honey), received a single dose of 5 ml honey intraperitoneally.Group 3(dexamethasone), received a single dose of 4.5 ml normal saline + 0/6 mg/kg dexamethasone (0/5ml) (OSVEH.IRAN. 8 mg/2 ml) intraperitoneally.

The abdominal incision was closed in two layers with continuous , simple sutures of polyglactin 910 (Vicryl®) & nylon 3/0 (SUPA.IRAN).In this study, a natural and pure alfalfa honey was used.This honey was produced in Kurdestan region of Iran. All rabbits were allowed to resume their diets until the 14^{th} postoperative day.

At the fourteen day after operation, 100 ml normal saline was instilled into the abdominal cavity of rabbits with a 16 G needle to improve the acoustic window. The number and density of adhesions sites were graded on the basis of ultrasonographic findings (Table 1). Sonographic evaluations were performed by Sonosite Titan, color ultrasonic doppler method diagnostic with linear probe in10 MHz frequency equipment.

All animals were sacrificed with over dose ethyl ether and the abdomen was opened. Adhesions were examined macroscopically and graded blindly according to the Blauer and Collins scale (Table 2).

The colon and abdominal wall tissue containing adhesions were excised en bloc and the sample were fixed in a 10 % formaldehyde solution. Samples were routinely processed and examined under a light microscope after H&E staining and then were evaluated by a pathologist to determine the general structure and the amount of fibroblastic activity and fibrosis present.Thus,the fibrotic score of each rabbit was calculated according to the criteria mentioned(Table3).

The Kruskal-Wallis test was used to test for differences in the grades of adhesions observed in the three groups. A Mann-Whitney U statistic analysis was used as a non-parametric test to determine differences in adhesion grading.

A P-value ≤ 0.05 was considered significant, and a P-value <0.001 was considered highly significant.All data were entered into and processed by SPSS 16 for Windows statistical package.

RESULTS AND DISCUSSION

The intra-abdominal adhesions and histopathological fibrosis scores are summarized in table 4.

In trans-abdominal sonogram, the adhesion to echogenic points was determined.

In grade 1, trans-abdominal sonogram showed echogenic bands in the abdominal cavity like mice-tail (Figure 1). In more serious subjects , the adhesions were so dense that the sonogram showed alveolate

echogenic masses or adhesion between viscera and abdominall wall (Figure 2). All the control and the dexamethasone groups and half of the honey group yielded positive sonographic findings(Figure 3).

Tabel 1: Adhesion assessment by ultrasonography. (Li *et al*, 2000 - Wang *et al*, 2003)

Grade	Description
0	No echogenic band
1	Echogenic bands in one area
2	Echogenic bands in two areas
3	Echogenic bands in three areas or alveolate echogenic bands in one area
4	Massive agglutinating adhesion or adhesion between viscera and abdominal wall

Tabel 2 : Blauer & Collins scale for macroscopic assessment of adhesion formation. (Blauer, 1998)

Grade	Description
0	No adhesion
1	Thin adhesive bands , easily separated
2	Thick adhesive bands limited to one area , separated by gravity
3	Extensive and thick adhesive bands , separated by traction
4	Extensive & thick adhesive bands and adhesions between viscera and /or abdominal wall, separated by sharp dissection

Tabel 3: Scale for microscopic assessment of fibrosis. (Yimaz *et al*, 2005)

Grade	Histopathological signs
0	No fibrosis
1	Thin bunches of a cellular fibrosis
2	Wide areas of fibrosis with reduced vascularization
3	Areas of fibrosis formed by thick bunch of collagen

Table 4: Intra abdominal , Ultrasonography adhesion and histopathological fibrosis score.

Group	Ultrasonography & Intra abdominal Adhesion score (M)	Fibrosis score (M)
1- Control	3.25 (2-4)	2.62 (2-3)
2- Dexamethasone	1.62 (1-3)	1.37 (1-2)
3- Honey	0.62 (0-2)	0.75 (0-2)

M = mean

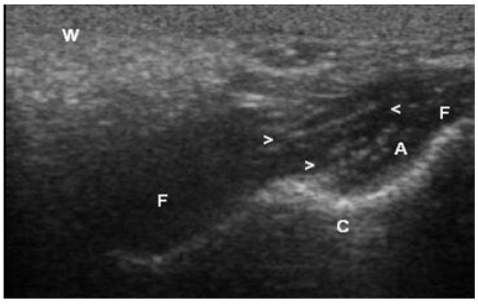

Fig. 1: Transabdominal sonogram showed the adhesion grade 1, The adhesion looks like a mouse tail (Group 3: Dexamethasone).
C: Colon, A: Adhesion, F: Fluid, W: Abdominal wall

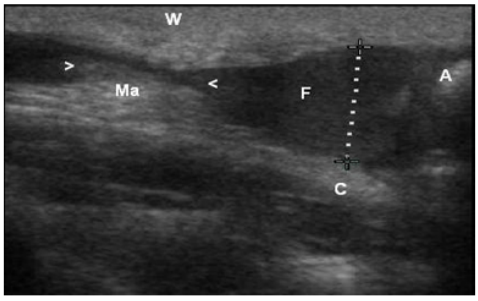

Fig. 2: Transabdominal sonogram showed the adhesion grade 4, Massive agglutinating adhesion between colon and abdominal wall (Group 1: Control).
C: Colon, F: Fluid, Ma: Massive agglutinating adhesion, A: Adhesion, W: abdominal wall

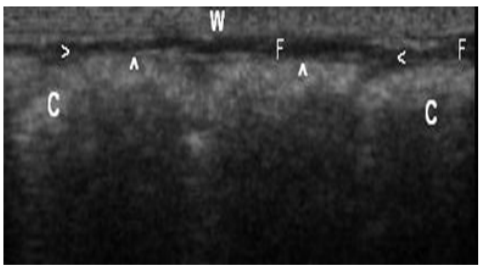

Fig. 3: Transabdominal sonogram showed no adhesion between colon and abdominal wall (grade 0). (Group 2: Honey).
C: colon, F: Fluid, W: abdominal wall

In dissection of eight rabbits in group 1(control), four developed grade 4 adhesions (Figure 4A), two developed grade 3 adhesions (figure 4B) and two developed grade 2 adhesions. In the group 2 (honey), one developed grade 2 adhesions, three developed grade 1 adhesions and four developed grade 0 adhesions.In the group 3 (dexamethasone), one developed grade 3 adhesions, three developed grade 2 adhesions (Figure 4C) and four developed grade 1 adhesions (Figure 4D). The control group had severe adhesion scores between organs or organs and abdominal wall.The honey group had fewer adhesive attachments to the intra-abdominal structures.The dexametasone group had moderate adhesion scores between organs.All the sonographic positive findings were proved to be the adhesion formation in dissection.

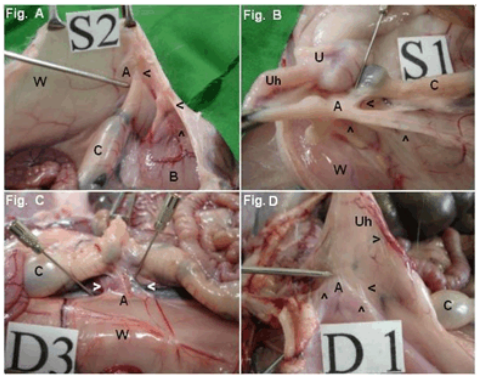

Fig. 4-A: Grade 4 adhesion, Adhesions (attachment) between the bladder – colon and the abdominal wall.
Fig. 4-B: Grad 3 adhesion, Extensive & thick adhesions between the colon and the uterin horn.
Fig. 4-C: Grade 2 adhesion, Thick adhesive band between the colon and the abdominal wall limited to one area.
Fig. 4-D: Grade 1 adhesion , thin adhesive band between the organ and the abdominal wall.
W: Abdominal wall, U: Uterus, Uh: Uterine horn, C: Colon, B: Bladder, A: Adhesion,
< ^ > : Areas of adhesion.

Compared to the control group, both the honey (p=0.001) and dexamethasone (p=0.005) groups exhibited a lower incidence of adhesion formation. Comparison of the honey and dexamethasone groups showed that adhesion formation was less severe in the honey group,but this difference was not significant (p=0.022).

Histopathological examination in the group 1(control) showed high amount of lymphocytes, severe increase in intestinal wall thickness and wide areas of fibrosis (Figure 5). The group2 (honey) showed severe decrease in the number of lymphocytes with considerable quantities of giant cells(Figure 6), normal intestinal wall thickness, mild fibrosis and increased angiogenesis (Figure 7).

The group 3(dexamethasone) showed considerable quantities of lymphocytes in the intestinal mucosa and sub mucosa, mild increase in intestinal wall thickness , moderate fibrosis and low amounts of angiogenesis.(Figure 8)

The honey group exhibited decreased fibrosis scores compared to the control group (p=0.001). The fibrosis scores in the dexamethasone group were also lower than the control group (p=0.002).However, there was no significant difference between the fibrosis scores of the honey and dexamethasone groups (p=0.069).

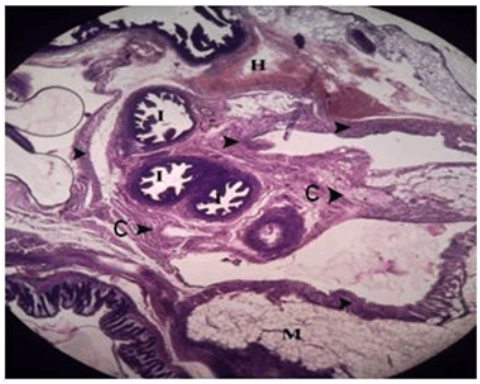

Fig. 5: Histopathological examination in the control group, showed high amount of connective tissue and wide areas of fibrosis (C), severe increase in intestinal wall thickness (I), Hemorrhage (H). (H&E staining)

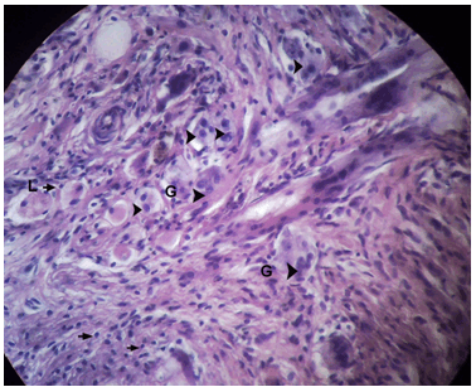

Fig. 6: Histopathological examination in the honey group, showed severe decrease in the number of lymphocytes (L) with considerable quantities of giant cells (G). (H&E staining)

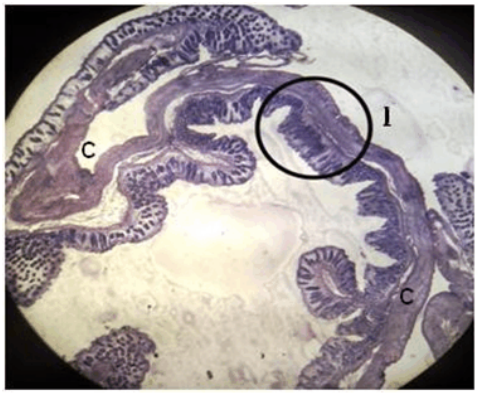

Fig. 7: Histopathological examination in the honey group, showed normal intestinal wall thickness (I), mild fibrosis and increased angiogenesis (C). (H&E staining)

Discussion:

Adhesion formation is a surface event associated with peritoneal wound healing.Abration and other peritoneal trauma leads to disruption of the mesothelium- the surface of which is extremely delicate- as its cells are loosely interconnected.Fibrin is then deposited at the damaged surfaces by bleeding and post-traumatic inflammation.This fibrin mass enlarges,reaching another tissue surface and forming a bridge between the tissue surfaces (Yilmaz *et al*, 2005 – Boland, 2006). Locally generated fibrinolytic factors are released that may degrade all or part of this fibrin bridge.However, surgical trauma, ischemia, inflammation, infection, thermal

or chemical injury, tissue desiccation and reactions to foreign materials such as sutures, gauze, glove powder, dramatically diminish fibrinolytic activity, in this case, fibroblasts and other cells may migrate across the bridge remnants, transforming it from the initially reversible fibrinous adhesion into a permanent adhesion with a connective tissue strauctur e (Imudia *et al*, 2008 - Yuzbasioglu *et al*, 2008). While the severity and extent of adhesions may change over weeks and months, the incidence of an adhesion is decided during the three to five days after peritoneal trauma takes place.

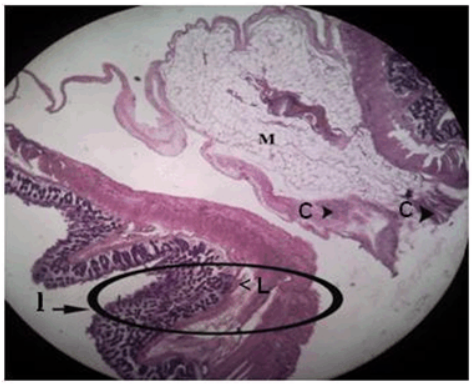

Fig. 8: Histopathological examination in the dexamethasone group, showed considerable quantities of lymphocytes in the intestinal mucosa and sub mucosa (L), mild increase in intestinal wall thickness (I), moderate fibrosis (C). (H&E staining)

Postoperative intra-abdominal adhesions can cause chronic pain, secondary female infertility, narrowing of digestive tract, intestinal obstruction, illeus, ureteral obstrauction and major source of postoperative morbidity(Van Der Krabben *et al*, 2000 - Emre *et al*, 2009).

Surgical dissection of adhesions is the common method for dealing with these complications, but adhesion reformation continues to be a problem. Adhesiolysis by laparoscopy and laparotomy can be very time-consuming, technically difficult and costly (Tittle *et al*, 2001).

During the past decade, different materials and methods have been suggested to prevent abdominal adhesions as lavage of abdominal cavity, Intraperitoneal administration of antibiotics, corticosteroid, nsaid, heparin, antihistamines, opioids, fibrinolytics and antioxidant agents, phospholipids and anti –adhesive barriers (bioresorbable membrane). The mechanical separation of peritoneal surfaces represents a strategy for blocking peritoneal adhesion formation (Wang *et al*, 2003 - Saribeyoglu *et al*, 2008 - Emre *et al*, 2009).

All of these materials have unique compositions and characteristics, with limitations and advantages regarding their use in the clinical setting. But so far, no ideal method has been found.

There are many experimental models for provoking peritoneal adhesions.The scraping model is very effective in engendering peritoneal adhesions because it involves two stages of damage, direct mechanical intestinal wall damage from gauze scraping and parallel incisions on the peritoneal layer of left abdominal wall. As this model mimics abdominal surgery, we chose to use it in this study (Singer *et al*, 1996 - Avsar *et al*, 2001).

Ultrasonography is a non-invasive and useful method in order to clinically diagnose and locate intra-abdominal adhesion. Peritoneal adhesion failed to be detected by routine ultrasonography. In order to improve the acoustic window, 100 ml normal saline was instilled into the abdominal cavity of rabbits. We employed this method to perform an assessment for the intra-abdominal adhesion (Li *et al*, 2000 - Wang *et al*, 2003). It was demonstrated that this method was visible and accurate, the score of intra-abdominal adhesion was well in agreement with that done by the dissection.

Systemic or intraperitoneal administration of corticosteroids has been reported to have conflicting effects on the prevention of peritoneal adhesions.Administration of corticosteroid directly on the damaged surface of the colon and abdominal wall - owing to its high concentrations and persistent effects - could effectively reduce the severity and incidence of adhesion, possibly by suppression of early inflammatory exudate and of late fibroblast invasion and proliferation (Avsar *et al*, 2001 - Zhang *et al*, 2002).

Natural honey is the foodstuff produced by honeybees from the nectar of flowers or secretions from other parts of the plant.Honey contains a wide range of enzymes,aminoacids,vitamins and trace elements in addition to readily assimilable sugars that stimulate tissue growth (White, 1975 - Gupta *et al*, 1992 - Emre *et al*, 2009).

Honey is an old agent that has seen renewed interest. Proposed benefits include enhancing wound debridement, reducing edema and inflammation, promoting granulation tissue formation – epithelialization and angiogenesis, and improving wound nutrition (Cooper, 1999 - Emre *et al*, 2009). It has an antibacterial effect through its enzymatic production of hydrogen peroxide from glucose.Honey increases collagen content, accelerates collagen maturation resulting from cross-linking, and maintains optimal pH conditions for fibroblast activity.

Honey is hygroscopic and hypertonic, and has a low pH. Hygroscopic substances decrease edema and constitute a fluid barrier to inhibit deepening of the wound. Hypertonicity contributes to antibacterial and antifungal properties (Erguder *et al*, 2008 - Emre *et al*, 2009 - Yuzbasioglu, 2009).

Mechanical separation of damaged peritoneal surfaces by honey, significantly decreased the development of postoperative intra-abdominal adhesion. This property is probably related to its high viscosity, hypertonicity and also late absorption of honey (Aljady *et al*, 2000 - Shokouhi *et al*, 2007 - Emre *et al*, 2009).

In the present study, a rabbit model was utilized to compare two types of anti-adhesive devices: honey and dexamethasone. It was concluded that intraperitoneal honey and dexamethasone decreases the incidence of postoperative intra-abdominal adhesion formation. Although the mechanism of this action is not clear, intraperitoneal administration of honey significantly reduced peritoneal adhesion formation without impairing the healing of wound.

Also the ultrasonography proved to be a useful tool to diagnose intra-abdominal adhesion, and its applications might be valuable to the clinical settings.

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