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EXPERIMENTAL STUDY

The effect of honey on the intestinal anastomotic wound healing in rats with obstructive jaundice

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Abstract: *Background:* Jaundice has been associated with an increased incidence of postoperative hernias, decreased wound and anastomotic bursting pressure, and reduced tissue collagen synthesis. This study is aimed to examine the possible effects of honey supplementation on anastomotic wound healing in obstructive jaundice (OJ) model.
Methods: Eighty wistar-albino rats were divided into four groups as control, OJ, O plus artificial honey and OJ plus honey. Rats were fed with standard rat chow (SRC) in group-I&II, SRC plus 10 mg/kg/day honey in group-4 and SRC plus artificial honey including the same caloric amount with honey in group-3. Colon anastomoses were performed in all groups. Also, common bile duct ligation was performed in group-1, group-2 and group-3. On the postoperative 3rd and 7th days, anastomotic healing was evaluated.
Results: The hydroxyproline level was significantly lower in the jaundiced animals compared with the controls and those given honey or artificial honey ($p<0.05$). The anastomotic bursting pressure results showed a correlation with the hydroxyproline results, and the use of honey significantly increased the bursting pressure compared with that of the bile duct ligated group ($p<0.05$).
Conclusion: The oral administration of honey can be considered when attempts at conventional internal drainage fail in obstructive jaundice *(Tab. 2, Fig. 6, Ref. 20)*. Full Text (Free, PDF) *www.bmj.sk.*
Key words: bursting pressure, gastrointestinal, honey, hydroxyproline, obstructive jaundice, wound healing.

It is well known that obstructive jaundice (OJ) has a deleterious effect on wound healing. Jaundice has been associated with an increased incidence of postoperative hernias, decreased wound and anastomotic bursting pressure, and reduced tissue collagen synthesis (1).

Honey is a super-saturated sugar solution produced by honey bees from the nectar of plants. It has been used as a reliable agent in wound healing since ancient times. Honey is sterile and inhibits the growth of both gram-positive and gram-negative bacteria (2). It is composed of several chemically active agents. Also physical properties like hygroscopicity, lower pH, and hypertonicity of honey are supposed to be responsible for its wound healing effect (2–4). Also, Erguder et al suggested that honey supplementation may give beneficial results in the prevention of hepatic damage induced by obstruction of the common bile duct (5).

This study was therefore designed to evaluate the effect of honey on the healing of intestinal anastomosis in rats with OJ.

Material and methods

The procedures followed in this study were in accordance with the *Guide for the care and use of laboratory animals* of the National Institutes of Health (Bethesda, Md.), and were approved by the Animal Ethics Committee.

Animals

A total of 80 male Wistar albino rats (*Rattus norvegicus*) weighing 230±25 g were housed on a 12-hour light/dark cycle and at a temperature of 21 C. The rats were accustomed to laboratory conditions 1 week before experimental use. They were housed one per cage under specified pathogen-free conditions with free access to water and standard rodent chow (Medas, Ankara, Turkey) except for 12 hours before the surgery.

Surgical procedures and groups

Sterile surgical protocols were maintained throughout the experiment. The rats were anaesthetized with IM ketamine (Ketalar, Parke Davis) 40 mg/kg and xylazine (Rompun, Bayer AG, Leverkusen, Germany) 5 mg/kg.

Group-1 (n=20) was the control group. Rats were fed with standard rat chow pre- and postoperatively. A 4-cm median laparotomy was performed under anesthesia. The left colon was transected (without any resection) 4 cm proximally to the peritoneal reflection. The bowel was restored by an end-to-end anastomosis with 6 interrupted, inverting sutures of 6/0 polypropylene (Prolene, Ethicon, UK). The abdominal wall was closed by continuous 3/0 polypropylene sutures (Prolene, Ethicon, UK). The animals were then randomly and equally divided into two subgroups, A and B, which were sacrificed on the postoperative days (POD) 3 and 7, respectively. Briefly, 6 cm of colon seg-

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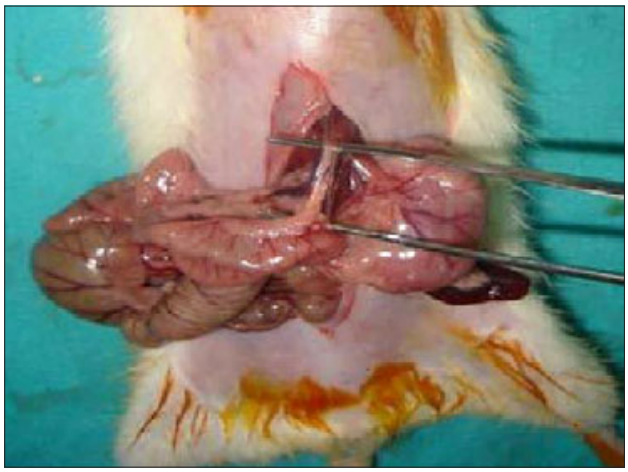

Fig. 1. Dissected common bile duct of the rat.

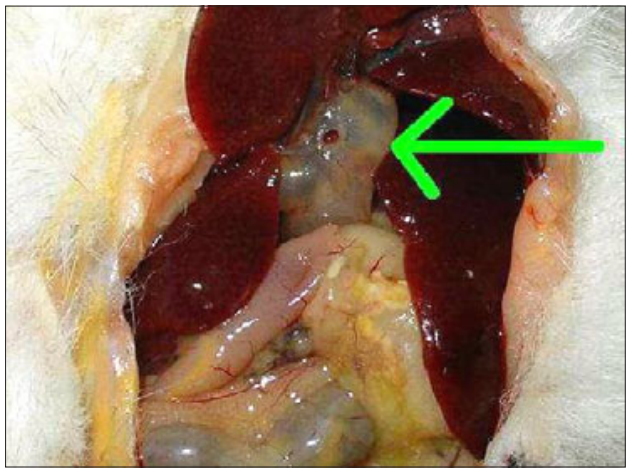

Fig. 2. Dilated bile duct (arrow) and jaundice.

ment centered by the anastomoses were resected just before the sacrification of each rat. Healing of anastomotic wounds was evaluated by measuring anastomotic bursting pressure, which is reported to be preferable to other methods, such as busting wall tension or tensile strength (6).

Group-2 (n=20) was the sham group. Rats were fed with standard rat chow pre- and postoperatively. The common bile duct (Fig. 1) was ligated and transected close to the duodenum. The abdomen was then closed with interrupted silk sutures. The rats were monitored for four days, as reported before (7), until an obstructive jaundice developed (Fig. 2) and then the second surgical procedure as in group-1 was performed. The animals were then randomly and equally divided into two subgroups, A and B, which were sacrificed on the POD 3 and 7, respectively. Briefly, 6 cm of colon segment centered by the anastomoses were resected just before the sacrification of each rat. Healing of anastomotic wounds was evaluated by measuring the anastomotic bursting pressure.

Group-3 was the second control group. Rats were fed with artificial honey, giving the same caloric amount as the honey, and standard rat chow pre- and postoperatively 7 days. The same surgical procedures as in the group-2 were performed. The animals were then randomly and equally divided into two subgroups, A and B, which were sacrificed on the POD 3 and 7, respectively. Briefly, 6 cm of colon segment centered by the anastomoses were resected just before the sacrification of each rat. Healing of anastomotic wounds was evaluated by measuring the anastomotic bursting pressure.

Group-4 was the study group. Rats were fed with the standard rat chow and 10 g/kg/day honey pre- and postoperatively 7 days. The same surgical procedures as in group-2 were performed. The animals were then randomly and equally divided into two subgroups, A and B, which were sacrificed on the POD 3 and 7, respectively. Briefly, 6 cm of colon segment centered by the anastomoses were resected just before the sacrification of each rat. Healing of anastomotic wounds was evaluated by measuring the anastomotic bursting pressure.

Honey and artificial honey were given by gavage once a day. The honey used in this study (Ferr) was obtained from Melis Ari Ciftligi Gida Sanayi ve Ticaret Ltd. Sti. Ankara, Turkey. Artificial honey was prepared by dissolving of 1.5 g sucrose, 7.5 g maltose, 40.5 g fructose and 33.5 g glucose in 17 mL sterile deionized water. The caloric amount of the honey used in this experiment was 325 kcal/100 g, so each rat in the groups 3 and 4 was given approximately 7.31 kcal/day extra calories by honey or artificial honey. The rats in the honey and artificial honey groups did not lose weight as those in the group-2. There were no statistically significant differences between the group-2 and group-3 and group-4. This might be due to the short duration of the study.

Anastomotic bursting pressure measurements

Measurements of the anastomotic bursting pressures were performed by another researcher except the surgeon in a blind fashion to the groups. Distal parts of the segments were closed with 2/0 silk sutures. The proximal parts of the segments were adapted to an intraluminal pressure manometer (monitoring kit L978-A07 Abott, Slingo, Ireland) and filled with isotonic NaCl solution with continuous infusion (4 mL/min). The bursting pressure (peek pressure before anastomotic disruption) was measured with a pressure transducer (peta, K 450, Ankara, Turkey). Since the evaluation of the bursting pressure might have caused damage along the anastomotic line, the anastomotic site was resected and divided into two parts vertically. One used for hydroxyproline measurement and the other placed in 10 % formaline for histopathological examination.

Measurements of the hydroxyproline levels

Hydroxyproline levels are shown to indicate the amount of collagen in tissues, and a direct relation between the anastomotic healing and tissue hydroxyproline levels has been reported (6). Hydroxyproline measurements were performed by another researcher in a blind fashion to the groups. The tissues (30–50 mg) were placed into hydrolysis tubes. 50 mM potassium phosphate buffer pH 7.0 and an equal volume of concentrated HCl were added to each tube, and the samples were hydrolyzed at 110 °C

Tab. 1. Histological grading scale (modified from (9)).

0	No evidence
1+	Occasional evidence
2+	Light scattering
3+	Abundant evidence
4+	Confluent cells or fibers

The following parameters were each assessed individually: inflammatory cell infiltration, blood vessel and fibroblast in growth, and collagen deposition.

for 16 hours. The samples were oxidized with Chloramine-T solution (pH 8.5), and the Ehrlich's reagent was added. The color was allowed to develop at 60 C for 25 minutes, and the absorbency at 560 um was determined with Bergman and Loxley's method (6). Total protein on tissue homogenates was determined by the addition of trichloroacetic acid (TCA, 10 % final concentration) to precipitate proteins, and the sample was centrifuged at 2500 *g* for 10 minutes. The amount of protein in the sediment was determined by a protein assay kit based on the Lowry method (Bio-Rad, Hercules, California). The hydroxyproline concentration was calculated as mg/g wet weight tissue.

Histological evaluation

After being stained with hematoxylene and eosin, colonic tissues and anastomosis were examined under light microscopy and were graded in a blind fashion, using a modified 0 to 4 numerical scale by Ehrlich and Hunt (8, 9) (Tab. 1). The evaluated parameters were the inflammatory cell infiltration, fibroblast ingrowth, neovascularization and collagen deposition. Each parameter was assessed individually using the numerical scale.

Statistical analysis

Statistical analysis was performed by the Statistical Package for Social Sciences (SPSS) 11.5 software (SPSS Inc., Chicago, IL, United States). Whether the continuous variables were normally distributed or not, this was determined by using the Shapiro Wilk test. Data were expressed as the median (25th–75th) percentiles. Because the data was non-normally distributed, the differences among the groups were evaluated by the Kruskal-Wallis test. When the p value from Kruskal-Wallis test was statistically significant, non-parametric multiple comparison test, was used to determine which group differ from others. The *p* value less than 0.05 was considered statistically significant.

Results

During the course of experimental protocols, there were no wound infections, intraabdominal abscess or anastomosis leakage as assessed by clinical inspection. One rat from group II and one from group III died in the early postoperative period probably due to anesthesia. On gross evaluation, no signs of anastomotic leakage, intraabdominal abscess, peritonitis or ileus were detected. No statistical significant differences between the mean weights of the groups were assessed during the entire study. This might be due to the short duration of the study. All results were summarized at Table 2.

Anastomotic bursting pressure measurements

On the POD 3, compared to the control group (35.5 mmHg (30.0–37.7)), obstructive jaundice (29 mmHg (26.0–32.2)) and OJ plus artificial honey treatment (31 mmHg (28.0–35.0)) resulted in a statistically significant decrease in the medians of anastomotic bursting pressure measurements ($p<0.05$). Compared to the sham group (29 mmHg (26.0–32.2)), honey treatment (35 mmHg (29.5–35.7)) resulted in a statistically significant increase in the medians of anastomotic bursting pressure measurements ($p<0.05$) (Fig. 3).

On the POD 7, compared to the control group (175 mmHg (170.0–177.0)), OJ (166 mmHg (160.0–170.5)) and OJ plus ar-

Tab. 2.Summary of the results.

	Group 1	Group 2	Group 3	Group 4	p[a]
Bursting pressure					
3rd Day	35.5 (30.0-37.7)	29.0 (26.0-32.2)[b]	31.0 (28.0-35.0)[b]	35.0 (29.5-35.7)[c]	0.012
7th Day	175.0 (170.0-177.0)	166.0 (160.0-170.5)[b]	170.0 (170.0-175.0)[b,c]	175.0 (170.0-175.0)[c]	0.003
Hydroxyproline					
3rd Day	2.8 (2.6-2.8)	2.1 (2.0-2.3)[b]	2.4 (2.2-2.6)[b,c]	2.5 (2.4-2.8)[c]	<0.001
7th Day	5.6 (5.5-5.8)	4.7 (4.2-4.9)[b]	5.1 (4.8-5.2)[b,c]	5.4 (5.2-5.5)[b,c,d]	<0.001
Inflammatory cells					
3rd Day	3.0 (3.0-4.0)	2.0 (2.0-3.0)[b]	2.0 (2.0-3.0)[b]	3.0 (3.0-3.2)[c,d]	<0.001
7th Day	3.0 (3.0-3.2)	3.0 (3.0-3.0)	3.0 (3.0-3.0)	3.0 (3.0-3.0)	0.605
Fibroblast ingrowth					
3rd Day	2.5 (2.0-3.0)	2.0 (2.0-2.0)[b]	2.0 (2.0-2.0)[b]	2.0 (2.0-3.0)	0.020
7th Day	2.0 (2.0-3.0)	2.0 (2.0-2.2)	2.0 (2.0-2.2)	2.0 (2.0-3.0)	0.603
Neovascularization					
3rd Day	1.0 (1.0-2.0)	1.0 (1.0-1.0)	1.0 (1.0-1.2)	1.0 (1.0-2.0)	0.348
7th Day	2.0 (2.0-2.2)	2.0 (2.0-2.0)	2.0 (2.0-2.0)	2.0 (2.0-2.0)	0.104
Collagen deposition					
3rd Day	1.5 (1.0-2.0)	1.0 (1.0-1.0)[b]	1.0 (1.0-1.0)[b]	1.0 (1.0-2.0)	0.012
7th Day	2.5 (2.0-3.0)	2.0 (1.0-2.0)[b]	2.0 (2.0-2.0)[b]	2.0 (2.0-2.2)[c]	0.002

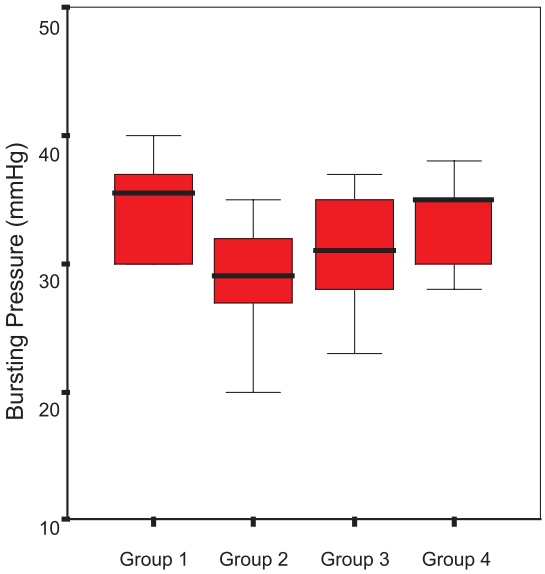

Fig. 3. Anastomotic bursting pressures (mmHg) of the groups on the postoperative 3rd day. There were statistically significant differences between control and Sham (p<0.05), control and group-3 (p<0.05) and Sham and group-4 (p<0.05). Median values were shown as black lines.

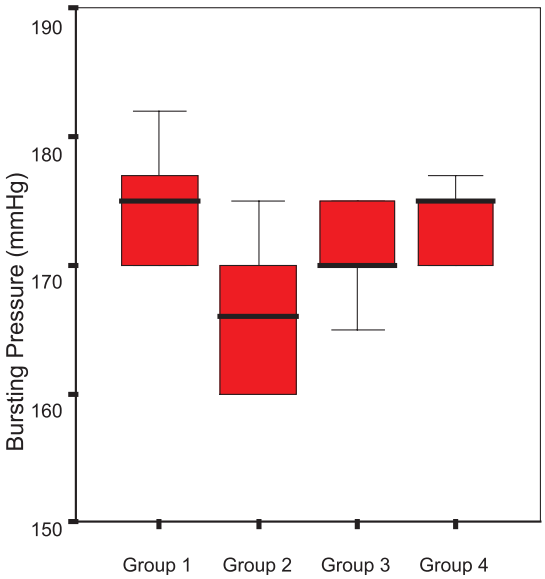

Fig. 4. Anastomotic bursting pressures (mmHg) of the groups on the postoperative 7th day. There were statistically significant differences between control and Sham (p<0.05), control and group-3 (p<0.05), Sham and group-3 (p<0.05) and Sham and group-4 (p<0.05). Median values were shown as black lines.

tificial honey treatment (170 mmHg (170.0–175.0)) resulted in a statistically significant decrease in the medians of anastomotic bursting pressure measurements (p<0.05). Beside this, compared to the sham group (166 mmHg (160.0–170.5)), artificial honey group (170 mmHg (170.0–175.0)) and honey treatment (175 mmHg (170.0–175.0)) resulted in a statistically significant increase in the medians of anastomotic bursting pressure measurements (p<0.05) (Fig. 4).

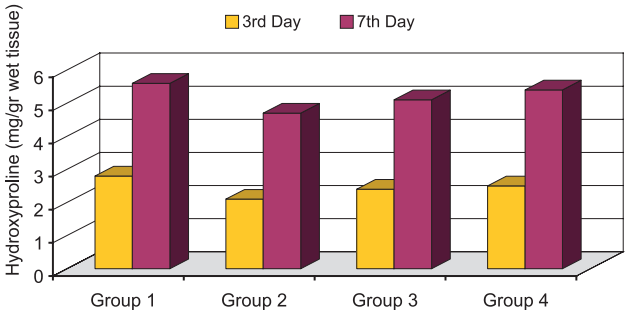

Fig. 5. Hydroxyproline levels (mg/gr wet tissue) of the groups. There were statistically significant differences between control and Sham (p<0.05), control and group-3 (p<0.05), Sham and group-3 (p<0.05) and Sham and group-4 (p<0.05) on the postoperative 3rd day. Also, there were statistically significant differences between control and Sham (p<0.05), control and group-3 (p<0.05), control and group-4, Sham and group-3 (p<0.05), Sham and group-4 (p<0.05) and group-3 and group-4 (p<0.05) on the postoperative 7th day.

Measurements of hydroxyproline levels

On the POD 3, compared to the control group (2.8 mg/gr wet tissue (2.6–2.8)), OJ (2.1 mg/gr wet tissue (2.0–2.3)) and OJ plus artificial honey treatment (2.4 mg/gr wet tissue (2.2–2.6)) resulted in a statistically significant decrease in the medians of tissue hydroxyproline levels (p<0.05). Beside this, compared to the sham group (2.1 mg/gr wet tissue (2.0–2.3)), artificial honey group (2.4 mg/gr wet tissue (2.2–2.6)) and honey treatment (2.5 mg/gr wet tissue (2.4–2.8)) resulted in a statistically significant increase in the medians of tissue hydroxyproline levels (p<0.05) (Fig. 5).

On the POD 7, compared to the control group (5.6 mg/gr wet tissue (5.5–5.8)), OJ (4.7 mg/gr wet tissue (4.2–4.9)) and OJ plus artificial honey treatment (5.1 mg/gr wet tissue (4.8–5.2)) resulted in a statistically significant decrease in the medians of tissue hydroxyproline levels (p<0.05). Beside this, compared to the sham group (4.7 mg/gr wet tissue (4.2–4.9)), artificial honey group (5.1 mg/gr wet tissue (4.8–5.2)) and honey treatment (5.4 mg/gr wet tissue (5.2–5.5)) resulted in a statistically significant increase in the medians of tissue hydroxyproline levels (p<0.05). Also, compared to the artificial honey group (5.1 mg/gr wet tissue (4.8–5.2)), honey treatment (5.4 mg/gr wet tissue (5.2–5.5)) resulted in a statistically significant increase in the medians of tissue hydroxyproline levels (p<0.05) (Fig. 3).

Histological evaluation

The common bile duct ligation resulted in bile stasis, necrosis and calcification of the colonic tissue (Fig. 6). On the POD 3, compared to the control group, OJ and OJ plus artificial honey treatment resulted in a statistically significant decrease in the medians of inflammatory cell infiltration, fibroblast ingrowth, and collagen deposition (p<0.05). Nevertheless, compared to the sham group, honey treatment resulted in a statistically signifi-

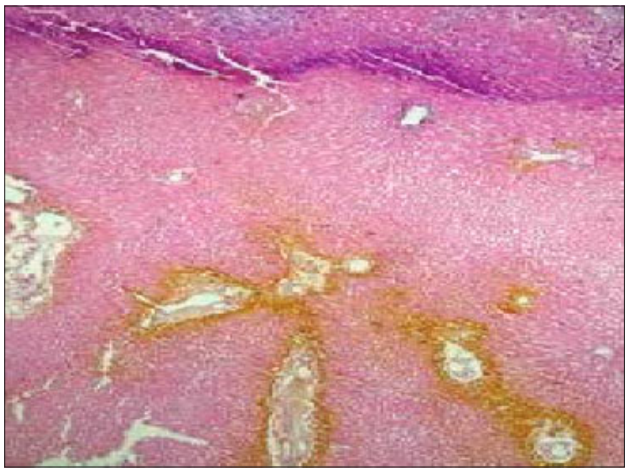

Fig. 6. Bile stasis, necrosis and calcification in colonic tissue in a rat from the group-2.

cant increase in the medians of inflammatory cell infiltration ($p<0.05$).

On the POD 7, although, compared to the control group, OJ and OJ plus artificial honey treatment resulted in a statistically significant decrease in the medians of collagen deposition ($p<0.05$), honey treatment resulted in a statistically significant increase in the medians of collagen deposition when compared to the sham group ($p<0.05$).

Discussion

Normal collagen synthesis is essential for the development of tissue tensile strength. The reason for the impaired wound healing in obstructive jaundice was initially explained by the theory that bilirubin or some other substances in the retained bile had an inhibitory effect on fibroblastic proliferation10, as in our study. However, recent studies have shown that the metabolic activities causing renal failure are also responsible for the impaired wound healing in obstructive jaundice. According to these in vivo and in vitro studies, TNF mediates endotoxin toxicity and regulates the fibroblast synthetic activities, including the inhibition of collagen and fibronectin production and the stimulation of collagenase (11, 12). In our study, on the POD 7, compared to the control group, OJ and OJ plus artificial honey treatment resulted in a statistically significant decrease in the medians of collagen deposition ($p<0.05$). However, honey treatment resulted in a statistically significant increase in the medians of collagen deposition when compared to the sham group ($p<0.05$). Nevertheless, in the medians of tissue hydroxyproline levels, calorical amount of the nutrition seems to be more effective in returning the negative effect of OJ to the wound healing on the POD 3 and POD 7 (Tab. 2). Nevertheless, on the POD 7, compared to the artificial honey group, honey treatment resulted in a statistically significant increase in the medians of tissue hydroxyproline levels ($p<0.05$) (Fig. 5). We did not come across any report about the effects of honey on tissue hydroxyproline levels in anastomotic wound healing. Further studies are needed to study the mechanism of this effect.

The physicochemical properties of honey not only contribute to its antibacterial properties but also to its wound healing capabilities. As in our study, with several ingredients and specific properties, honey possesses a broad spectrum of effect: it has antifungal, cytostatic, anti-inflammatory effects and promotes wound healing (13). Also, it is shown that oral (13) and local (14) application of honey reduces postoperative intraperitoneal adhesion formation. In this study, we showed that honey treatment may be effective in reversing the adverse effects of OJ on the anastomotic wound healing.

Schramm et al found that phenolic antioxidants from the processed honey were bioavailable (15), and they increased the antioxidant activity of plasma. Gheldof et al also showed that the in vivo serum antioxidant capacity increased significantly following a consumption of buckwheat honey in human (16). These studies showed that the antioxidant effect of honey was not only local, but also had a systemic effect. The antioxidant capacity of honey appeared to be a result of the combined activity of a wide range of compounds including phenolics, peptides, organic acids, enzymes and Maillard reaction products (17). In the medians of anastomotic bursting pressures, honey treatment seems to be more effective in returning the negative effect of OJ to the wound healing on the POD 3. But, the calorical amount of the nutrition seems to be more effective in returning the negative effect of OJ to the wound healing on the POD 7 (Tab. 2). Also, medians of anastomotic bursting pressures on the POD 7 were found better in artificial honey and honey treatment groups than in the control group by Gollu et al (13). But, we did not come across any report about the effects of honey on the early anastomotic wound healing. Thereby, this is also the first study about the effects of honey treatment on the early anastomotic wound healing. Further studies are needed to study the mechanism of these effects.

The anti-inflammatory action of honey has been studied, but no definite mechanism has been identified. Honey provides a glucose supply for leucocytes. It also provides substrate for glycolysis, which is the major mechanism for the energy production in the macrophages. Honey may modulate the activation state of immunocompetent cells within the wound. These data suggest that honey may have a number of effects on the molecular mechanisms of wound healing (18).

Assimakopoulos et al (19) studied the oxidative alterations in the intestinal mucosa of patients with obstructive jaundice and found that obstructive jaundice in humans induced the intestinal oxidative stress, which might be a key factor contributing to intestinal barrier failure and the development of septic complications in this patient population. In the light of the results of studies about the antioxidative effects of honey and intestinal oxidative stress in obstructive jaundice, we concluded that the protective effect of honey on intestinal anastomosis, in our study, might be attributable to the antioxidative effects of honey. Since we studied only the effect of honey on the intestinal anastomotic wound healing in rats with obstructive jaundice, not the mecha-

nism of this effect, we did not evaluate the oxidative stress parameters. These parameters should be analyzed in further studies evaluating the mechanism of these effects.

In the previous study, hydroxyproline concentration was used as a marker of collagen synthesis and was found to be reduced in animals with an obstructive jaundice (20). In the present study, the hydroxyproline level was significantly lower in the jaundiced animals compared to the controls and those given honey or artificial honey. The anastomotic bursting pressure results showed a correlation with the hydroxyproline results, and the use of honey significantly increased the bursting pressure compared to that of the bile duct ligated group.

Thus, it appears that the absence of bile acids in the bowel triggers reactions resulting in impaired wound healing. To relieve biliary obstruction and the resulting portal endotoxemia, internal biliary drainage should be the first choice of treatment to reduce postoperative complications. However, the oral administration of honey can be considered when attempts at conventional internal drainage fail. Further studies are needed for the evaluation of the exact mechanism.

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