International Journal of Surgery 8 (2010) 121–127

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.theijs.com

Effect of honey versus intergel in intraperitoneal adhesion prevention and colonic anastomotic healing: A randomized controlled study in rats

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ARTICLE INFO

Article history:
Received 16 September 2009
Received in revised form
18 October 2009
Accepted 17 November 2009
Available online 2 December 2009

Keywords:
Honey
Peritoneal adhesion
Colonic anastomosis
Rats

ABSTRACT

Introduction: Intra-abdominal adhesion formation and reformation after surgery are still an unavoidable event in spite of modern surgical techniques and are a cause of significant morbidity, resulting in infertility, pain and intestinal obstruction.
Aim: To investigate the effect of honey in adhesion prevention and colonic anastomotic healing in rats.
Methods: In the present study, 75 male Sprague–Dawley rats were used and divided into 3 groups for study: [25 rats for each], the intergel, honey and control groups. After the scheduled two-week's post-operative period, all survived rats were reopened for second-look laparotomy to detect the following parameters: a – adhesion, b – manometric study, c – histopathological study.
Results: The author found that the total adhesion score, the manometric values and the histopathological study among the three studied groups showed statistically significant difference and in favor of the honey-treated rats.
Conclusion: Honey surpasses the intergel for the healing power and adhesion prevention.

1. Introduction

Intra-abdominal adhesion formation and reformation after surgery are still unavoidable events in spite of modern surgical techniques[1] and there is no satisfactory treatment or prophylaxis to deal with these adhesions properly.[2] Because wound healing and adhesion formation have similar pathways, modulation of the release factors could be expected to affect adhesion formation.[3,4]

Abdominal surgery frequently includes the construction of a bowel anastomosis which carries the risk of symptomatic anastomotic leakage with subsequent increasing mortality rate up to 20%.[2] It was stated that operative trauma and surgical manipulation[2,3] as well as ischaemia of the traumatized tissues induce peritoneal mesothelial damage with the result of extravasation of fibrin which will be removed by the process of fibrinolysis.[5,6] Various methods have been tried to reduce post-operative adhesions including mechanical separators and barriers such as carboxymethylcellulose, oxidized regenerated cellulose and bioresorbable membrane based on a chemically modified form of hyaluronic acid and carboxymethylcellulose,[2,6,9] fibrinolytic agents as recombinant tissue plasminogen activator, anti-coagulants like heparin, and non steroidal anti-inflammatory drugs.[6,7]

Hyaluronate enhanced the fibrinolytic response of the human peritoneal mesothelial cells and adhesion prevention.[8,9] Intergel, is an ionically cross-linked 0.5% ferric hyaluronate supplied in the gel form.[10] Indeed, Honey was proved effective as anti-adhesion agent in experimental animals.[11–13] It was observed clinically that healing in open wounds is faster with honey rendering wounds suitable for suture.[14]

2. Research aim

The aim of the present study is to investigate the effect of HONEY in adhesion prevention and colonic anastomotic healing in rats.

3. Materials & methods

3.1. The animals

75 healthy male Sprague–Dawley rats having average weight 250–300 g were divided into 3 groups for study: [25 rats for each], honey, intergel, and control groups. Rats were obtained from the documented animal house of the faculty of veterinary medicine, Suez-Canal University, Egypt. Rats were housed and fed a standard laboratory diet and water *ad libitum* up to 2 pm. Animals were fasted, except for water, for 12 h before the surgical intervention. Neither mechanical bowel preparation nor intraoperative bowel irrigation were performed.

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1743-9191/$ – see front matter
doi:10.1016/j.ijsu.2009.11.010

The local ethics committee for the use of laboratory animals approved all experimental procedures. Appropriate animal care and use were performed according to implementation and compliance with the Animal Welfare Act.

3.2. Tested materials

3.2.1. Intergel

Intergel (Johnson & Johnson, Egypt) is a sterile 0.5% Ferric Hyaluronate in gel form, packed in a compressible plastic bottle as 300 ml volume to be used for the adult patient. For purpose of standardization, honey was obtained from a single source and was subjected to a process of purification and filtration to remove insect particles and other debris and then diluted (50%) with distilled water.[11,12]

3.2.2. Honey

Honey is 18–20% water and is comprised of glucose, fructose, vitamins A, B-complex, C, D, E, K, and β-carotene, as well as minerals, antioxidants, amino acids, and enzymes. Honey contains phenolic compounds and the enzyme glucose oxidase, which becomes active when honey is diluted and produces hydrogen peroxide. Honey was obtained from the farm of faculty of veterinary medicine, Suez-Canal University, Egypt **and was** used after being purified by the use of a special filter allowing separation of insect particles, spores and debris.[11,12] This step for filtration of honey was conducted in the laboratory of surgical department, faculty of veterinary medicine, Suez-Canal University.

4. Methods

4.1. Anesthesia

General anaesthesia was induced with intramuscular Ketamine (50 mg/kg) and Xylazine (6 mg/kg).[4–6] This was conducted by a specialized team work of the department of surgery & anaesthiology in the faculty of veterinary medicine Suez-Canal University.

4.2. Surgical procedure

The researcher, under strict antiseptic condition, performed all surgical procedures. End-to-end single layer extramucosal anastomoses were created with eight interrupted 6/0 prolene. Haemostasis was secured and any residual blood even so minute was removed completely and gently. No drain was left and the abdominal wound was closed in two layers with continuous 3/0 silk sutures.

4.3. Instillation of tested materials

The tested materials, 3 ml of honey and intergel were instillated, using sterile syringes; into the abdominal cavity before completing laparotomy wound closure to prevent escape of the material outside the peritoneal cavity.

4.4. Post-operative period

All rats were observed in the post-operative period and data was collected day by day and saved as soft–wear files for later evaluation. After the scheduled two-week's post-operative period,[11] all survived rats were reopened for second-look laparotomy to detect the following parameters: a – adhesion, b – manometric study c – histopathological study.

4.4.1. Study of adhesion formation

Subsequently, adhesion formation was scored blindly by two independent observers unaware of the groups. Two parallel systems were used to evaluate both the ***degree*** of severity and the ***extent*** of adhesion. As regard to the degree of severity of the formed adhesions in all groups, the 4-point scale system was used: grade 0: no adhesions, grade 1: thin, few and filmy, grade 2: thick and avascular and grade 3: thick, vascular and extensive.[15] As regard to the extent of adhesion formation in all groups the 4-point scale system was used: 0 = none, 1 = localized, 2 = moderate and 3 = extensive.[16,17]

4.4.1.1. Calculation of the total adhesion scores. The total adhesion score for each animal was the sum of these two scores (extent and severity), with a maximum total score of 6.

4.4.2. Manometric study

Manometric study of the effect of the tested materials on the anastomotic integrity was performed by detecting both of bursting pressure and breaking strength. A simple manometer was used to evaluate the anastomotic integrity. It is in the form of a mercury-graduated manometer connected to an air insufflator.[5]

4.4.2.1. Detection of bursting pressure. Bursting pressure is the minimal force exerted to cause anastomotic perforation and was measured as previously reported.[16,18]

4.4.2.2. Detection of breaking strength. Breaking strength is the maximal force needed to disrupt the anastomosis.[16] After determination of the bursting strength, the breaking strength was measured in the same segment after sealing the perforation with mosquito forceps.

4.4.3. Histological study

Hematoxylin and Eosin (H&E) stain is the most widely used in general-purpose stain combination and was used for staining colonic segments subjected to histological study.[16] The author used this descriptive system of histological grading the healing process by modifying some of its parameters to accommodate with our study. The suggested system was given a 3-point for scoring with the upper scoring degree was 12 points and the under was 4 points:

1- Mucosal healing: 1 point for no epithelialization, 2 points for attempt at epithelialization and 3 points for glandular formation.
2- Inflammatory cell exudate: 1 point for heavy infiltration, 2 points for moderate infiltration and 3 points for mild infiltration.
3- Fibroblastic activity: 1 point for mild infiltration, 2 points for moderate infiltration and 3 points for heavy infiltration.
4- Neo-capillary formation: 1 point for mild infiltration, 2 points for moderate infiltration and 3 points for heavy infiltration.

4.5. Statistical analysis

The statistical tests were run on a compatible personal computer using the Statistical Package for Social Scientists (SPSS) for windows 9. The values were expressed as means ± standard errors of deviation. The mean values of the groups were compared by one-way analysis of variance (ANOVA) as well as the least significant difference (Tukey's Honestly Significant Difference) as a post hoc test. $P < 0.05$ was considered significant.

5. Result

5.1. Adhesion

5.1.1. Extent of adhesion

Adhesion extent was given a score value as the 4-point grading system [values 0–3]: no adhesion [value = 0], localized adhesion