



Effects of Preoperative Honey Drink on Gastric Content, Perioperative Discomfort and Insulin Resistance in Patients Undergoing Open Colorectal Surgery a Randomized, Controlled Trial

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Authors' contributions

This work was carried out in collaboration between all authors. Author Sudiyatmo designed the study, managed the literature search, wrote the draft of the manuscript and performed the research. Author MIR performed the surgery and supervised the work. Author NP performed the anesthesia and supervised the work. Author NIL performed the statistical analysis and also wrote part of manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background and Aims: Preoperative fasting and surgery cause uncomfortable condition, metabolic stress and insulin resistance for the patient. A recent study in colorectal patients indicates that even small elevations of insulin resistance increase the risk of complications. Preoperative carbohydrate can reduce perioperative discomfort and insulin resistance. We investigated the effects of honey as preoperative carbohydrate-rich drink on the residual gastric contents,

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perioperative discomfort, and insulin resistance.

Methods: Randomized, prospective, controlled study. Thirty colorectal cancer patients who underwent elective open colorectal surgery were randomized and divided into the treatment or control group. Patients in treatment group ($n = 15$) received 250 ml water containing 50 ml honey on the evening and 2-3 hours preoperatively. Control patients ($n = 15$) underwent overnight fasting. Three different discomfort variables (thirst, hunger and tiredness), residual gastric content, plasma glucose, insulin concentrations and insulin resistance index were recorded during the perioperative period.

Results: Patient and operative characteristics did not differ between groups. There was no statistical difference between the two groups with respect to gastric residue content. Subjective well-being was significantly better in the treatment group. Plasma glucose, serum insulin levels and insulin resistance index were found to remain significantly lower in the treatment group.

Conclusion: The preoperative honey drink does not appear to alter the volume of residual gastric contents, suggesting that this is safe procedure. Preoperative honey intake is advantageous due to reducing perioperative discomfort and insulin resistance.

Keywords: Preoperative fasting; insulin resistance; preoperative carbohydrate-rich drink; honey; open colorectal surgery.

1. INTRODUCTION

Conventional preoperative fasting is still a routine procedure in many institutions to avoid regurgitation and aspiration of gastric content during the perioperative period [1]. In addition, this procedure can be excessively long lasting from 10 up to 16 hours. The overnight fasting is long enough to deplete liver glycogen store and is also uncomfortable for the patient [2]. Preoperative fasting and surgery initiate a series of stress physiological process in the body, inducing transient insulin resistance [3]. Insulin resistance is a key factor of the postoperative metabolic response to surgical injury [4]. The main feature of insulin resistance is a hyperglycemia state, due to increasing glucose and reducing insulin stimulated glucose uptake in liver and peripheral [5]. In major surgical procedures, such as major colorectal operations, up to 90% of the preoperative insulin sensitivity can be lost after the operation [6].

Intake of oral carbohydrate may improve postoperative metabolic response, insulin resistance and reduce recovery time. Furthermore, it has been reported to improve subjective well-being by reducing perioperative thirst, hunger, and tiredness [6]. For this purpose, a carbohydrate-rich beverage was developed (12.5% carbohydrate, 285 mOsm) for preoperative use. This solution contains water, maltodextrin, fructose and provides 50 kcal/100 ml energy [7].

Honey is a natural product and source of sugars. The main sugars in honey are fructose and

glucose. They are absorbed directly into the blood, provide a rapid source of energy without the need of digestion. Moreover, there are several effectiveness of honey in gastrointestinal disorders, wound healing and as an antibacterial and antiinflammatory agent [8]. It is a natural source of readily available carbohydrates and may serve as an inexpensive alternative of preoperative carbohydrate rich drink.

In this study, we evaluated the safety of honey drink as preoperative oral carbohydrate loading in patients undergoing elective open colorectal surgery and the effects of preoperative honey drink on residual gastric content, perioperative discomfort (thirst, hunger, and tiredness), insulin resistance and the incidence of wound infection. In addition, we aimed to establish current guidelines for the preoperative management of surgical patients at our center.

2. MATERIALS AND METHODS

Randomized, prospective, controlled trial was conducted between November 2014 to April 2015 in the Dr. M.Djamil Hospital, Padang. The study protocol was approved by the Institutional Ethics Committee, Faculty of Medicine at Andalas University. Before being enrolled in the study, each patient was informed about the aim and method of the study, including details of the treatment procedure, and a written consent was obtained.

Subjects were 32 colorectal cancer patients who underwent elective open colorectal surgery. Inclusion criteria includes adults (20-70

years-old), body mass index (BMI) 18-30 and candidates to elective open colorectal surgery. Exclusion criteria were gastro-esophageal reflux, intestinal obstruction metabolic disease including diabetes mellitus or impaired glucose tolerance, American Anesthesiologists Association (ASA) score above 2, renal or hepatic insufficiency. Patients with any non-compliance with the study protocol, or presented significant intraoperative occurrences, or experienced prolonged operations (lasting more than 4 hours) were also excluded. Height and weight for each individual was measured and body mass index calculated.

The patients were randomised and divided into two groups (n = 16 patients in each group). The treatment group was prepared with honey drink and the control group fasted from the midnight. Patients in treatment group received 250 ml water containing 50 ml honey on the evening before operation and the same fluid 2-3 hours before surgery. Before surgery, all patients did not have enteral or parenteral nutritional support, and they have the same preoperative bowel preparation.

Three perioperative discomfort variables (thirst, hunger, and tiredness) were evaluated with a 100-mm visual analogue scale (VAS) at 30 minutes before induction of anesthesia and 4 hours after surgery. Patients were asked by one investigator, to grade the degree of thirst, hunger, and tiredness (VAS 0, extremely light; VAS 100, extremely severe).

Evaluation of residual gastric content was carried out in the operating room just before the initiation of surgery. A nasogastric tube 16 fr was placed immediately after anesthesia induction, and its

correct position was confirmed by auscultation. The investigator performed aspiration of gastric content and total volume were recorded.

In order to measure blood glucose and insulin concentration, peripheral venous blood samples were collected both at 30 minutes before induction of anesthesia and 4 hours after surgery. Blood glucose concentration was measured by using an automatic biochemistry analyser. Blood samples were centrifuged immediately for 10 minutes to separate the plasma. The plasma was stored at -80°C until measurement on insulin. Plasma concentration of insulin were measured with enzym-linked immunosorbent assay (ELISA) method. The insulin resistance assessed by the HOMA-IR equation (Homeostasis Model Assessment-Insulin Resistance). $HOMA-IR = \text{Insulin } (\mu\text{U/ml}) \times \text{blood glucose (mg/dl)} / 405$. A complication was defined as postoperative wound infection. This event was observed and documented on medical record. The total number of wound infections which occurred were determined.

2.1 Statistical Analysis

SPSS 17.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analyses. Patient characteristics were analyzed with unpaired t-test. The perioperative discomfort variables are presented as median (min-max). VAS measurements were analyzed with Mann-Whitney U-test between groups. The data of glucose, insulin, and insulin resistance are presented as means ± standart deviation (SD). Intergroup differences were analyzed with Mann-Whitney U-test. *P* value < 0,05 considered statistically significant.

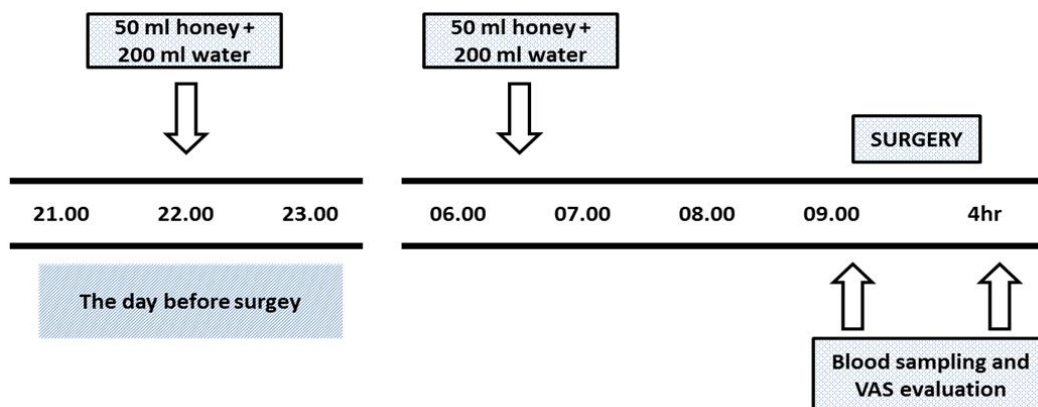


Fig. 1. Timeline of preoperative honey drink consumption

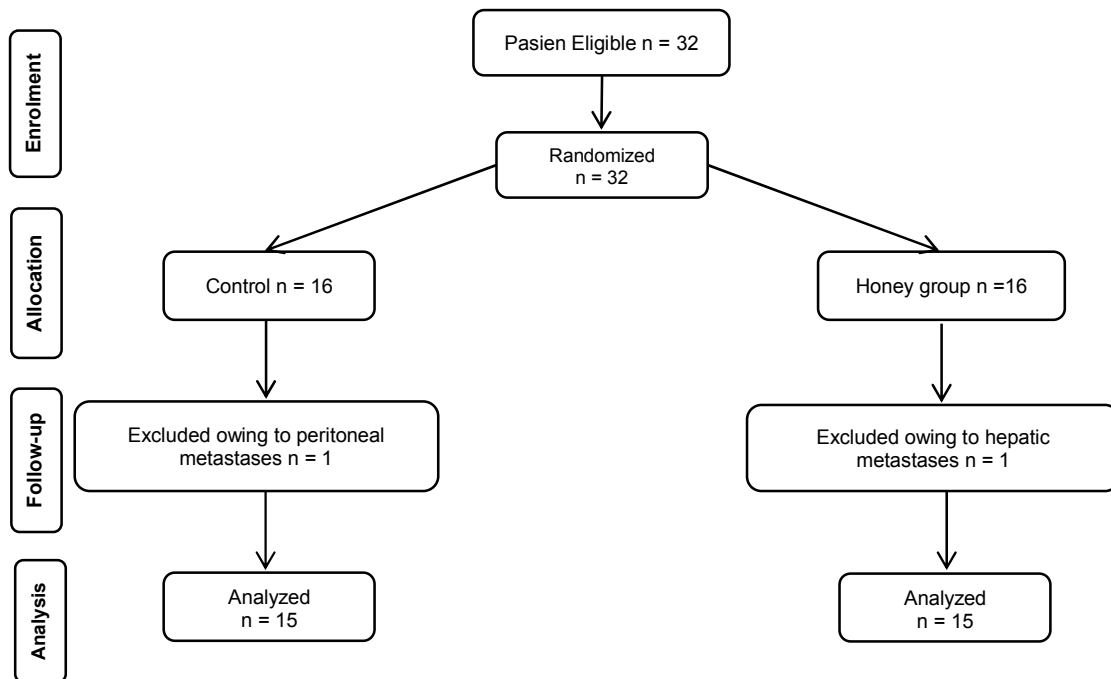


Fig. 2. Flowchart of randomization

3. RESULTS

Thirty two patients were eligible and included for randomization. Of these 32 patients, two did not complete the study because of hepatic and peritoneal metastases discovered at operation. Fifteen patients, in each group remained for analysis. The age distribution was similar in the two groups; the control group's mean age was $43,9 \pm 13$ years, and the treatment group's mean age was $53,7 \pm 13$. Two groups were comparable with regard to age, sex, body mass index (BMI), duration of surgery, and type of operation. There was no statistically significant difference for demographic and surgical characteristics between control and treatment group (Table 1).

The subjective discomfort of patients according to the VAS rating and preoperative residual gastric volume are shown in Table 2. At 30 minutes before anesthesia induction, patients in the honey group felt significantly less thirst ($P = 0,001$), hunger ($P = 0,023$) and tiredness ($P = 0,029$) compared with that in control group. At 4 hours after surgery, patients in the control group felt significantly more thirst ($P = 0,001$) and hunger ($P = 0,033$), but there was no significant differences in median VAS scores for tiredness between the groups ($P = 0,187$). The median

residual volume of gastric contents were similar in two groups ($P = 0,653$). No cases suspected pulmonary aspiration or regurgitation related to oral intake were noted following preoperative honey drink.

At the 30 minutes before anesthesia, blood glucose levels were no differences between the two groups ($P = 0,162$). However, honey drink group showed lower blood glucose levels when compared to control group postoperatively (140 ± 26 mg/dl vs 223 ± 71 mg/dl, $P = 0,001$). Preoperatively, the values of serum unsulin (8 ± 3 vs $12,7 \pm 7,5$ with $P = 0,006$) and insulin resistance ($1,8 \pm 0,5$ vs $3,4 \pm 1,9$ with $P = 0,004$) were significant lower in the honey drink group than in the control group. In the comparison between the alterations occurring in the two groups, between pre and postoperative, insulin and insulin resistance were significant increase in the control group, which can be clearly seen in Table 3. In regards to the total number of wound infections, patient in the control group tended to experience more wound infections compared to the honey group (4 vs 1, $P = 0,068$).

4. DISCUSSION

There were two most important findings in this study. First, preoperative honey drink reduced

various discomfort parameters (thirst, hunger and tiredness) compared with overnight fasting in patients undergoing elective open colorectal surgery. Second, the present data show that patients given honey drink shortly before surgery, display less impaired insulin sensitivity as compared to patients operated after an overnight fast.

Reducing the length of preoperative fasting are among the issues that have drawn attention in more recent studies [9]. Ingestion of clear fluids

does not give rise to increased risk for aspiration of gastric content and is allowed until 2 hours before surgery. A recent randomized controlled trial found no significant difference in gastric residual content between patients given 400 ml carbohydrate-rich fluid 2 hours before surgery and those who were fasted overnight [10]. In agreement with previous reports, in our study, we identified no significant difference in the gastric residual volume between those who received preoperative honey drink versus those who underwent overnight fasting.

Table 1. Demographics data of the patients in the two groups

	Control (n=15)	Honey drink (n=15)	P value
Age (years)	43,9±13	53,7±13	0,351*
Sex			
Male	9 (30%)	11 (37%)	0,350
Female	6 (20%)	4 (13%)	
Body mass index (kg/m ²)	20,7±2,1	19,8±2	0,266*
Duration of the operation (min)	193±36	186±24	0,521*
Operative procedure			
Abdominoperineal resection	3	3	
Anterior resection	5	6	
Colectomy	4	5	
Sigmoid colectomy	3	1	

*Data are presented as mean ± SD

Table 2. Visual analogue scale (VAS) data for perioperative discomfort variables and preoperative residual gastric volume

VAS variable	Time	Control	Honey drink	P value
Thirst	30 min BI	30 (20-40)	20 (10-30)	0,001
	4 h AS	70 (40-80)	50 (40-60)	0,001
Hunger	30 min BI	20 (10-30)	20 (10-20)	0,023
	4 h AS	50 (40-60)	50 (40-60)	0,033
Tiredness	30 min BI	20 (10-30)	10 (10-20)	0,029
	4 h AS	60 (40-70)	50 (40-70)	0,187
Gastric Volume (ml)	BS	5 (0-15)	5 (0-25)	0,653

Data are presented as median (min-max); 30 min BI = 30 minutes before induction of anesthesia
4 h AS = 4 hours after surgery; BS = between induction of anesthesia and surgery

Table 3. Perioperative blood glucose, insulin, insulin resistance and wound infection in the two groups

Variable	Time	Control	Honey drink	P value
Glucose (mg/dl)	30 min BI	105±24	94±15	0,162
	4 h AS	223±71	140±26	0,001
Insulin (µIU/ml)	30 min BI	12,7±7,5	8±3	0,006
	4 h AS	22,6±13,5	9,8±2,9	0,000
Insulin resistance (HOMA-IR)	30 min BI	3,4±1,9	1,8±0,5	0,004
	4 h AS	10,1±5,5	3,3±1	0,000
Wound infection		4	1	0,068

Data are presented as mean ± SD; 30 min BI = 30 minutes before induction of anesthesia;
4 h AS = 4 hours after surgery

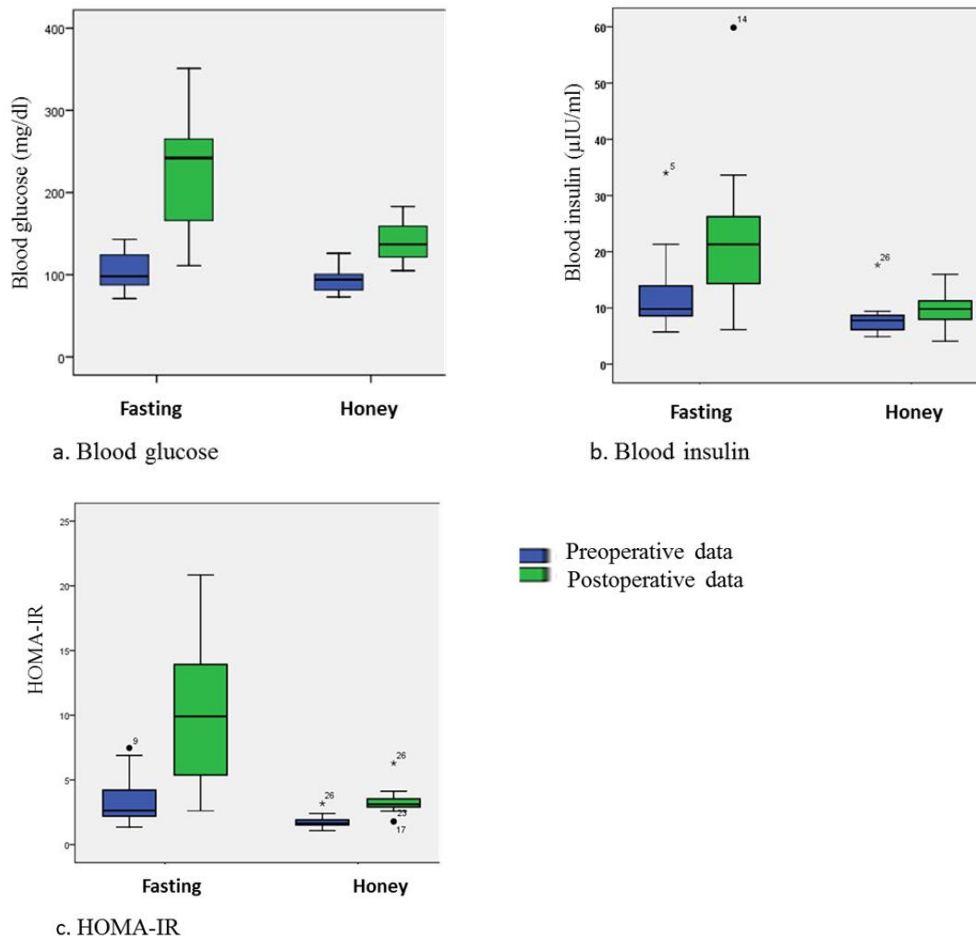


Fig. 3. Perioperative blood glucose, insulin and insulin resistance in the two groups: a. Blood glucose (mg/dl); b. Insulin (µIU/ml); c. Insulin resistance (HOMA-IR)

The result of the blood glucose (after surgery), insulin and HOMA-IR were significantly lower in the honey group, before and after surgery ($P < 0,05$)

Compared to the control group, patients in the honey group were less thirsty and hungry even 30 minutes before anesthesia and 4 hours after surgery. Although, differences in tiredness after surgery were not significant, preoperative honey drink appeared to slightly reduce tiredness preoperatively. This is likely to be remaining effect of the morning dose of honey drink on 2-3 hours before surgery. Hausel et al. have randomized 252 elective surgery patients to preparation with carbohydrate rich drink, placebo and overnight fasting. They reported that thirst and hunger were reduced by preoperative consumption of a carbohydrate drink [11]. Shorter fasting time can reduce discomfort associated with a surgical procedure, thus preoperative honey drink can reduce the stress experienced by patient before and after surgery.

Starvation has been shown to induce insulin resistance in healthy subjects [12]. Fasting from the previous evening inhibited insulin secretion and the glycolysis system was enhanced in the morning of the operation day, resulting in an increase in the plasma glucose level. Intake of carbohydrate rich drink prevented the increase in the plasma glucose level by endogenous release of insulin and improved insulin sensitivity perioperatively [2]. In this study, the conventional fasting was associated with higher glucose and insulin levels. The results in our study are consistent with previous reports, on lower of plasma glucose, insulin and insulin resistance after drink preoperative carbohydrate-rich fluid. Wang ZG, et al. [13] reported that preoperative oral carbohydrate reduces insulin resistance after open radical resection of colorectal cancer.

Carbohydrate group was given a 400 ml carbohydrate rich drink (12.5% carbohydrate, 0.5 kcal/ml) 3 hours before induction of anaesthesia.

Insulin resistance is a key factor of the postoperative metabolic response to surgical injury [4]. The main feature of insulin resistance was a hyperglycemia state, due to increasing glucose and reducing insulin stimulated glucose uptake in liver and peripheral (mainly skeletal muscle) [5,14]. Nonetheless, development of hyperglycemia has been shown to be associated with increased morbidity and mortality [15]. The recent study showed that the degree of insulin resistance when the patient was leaving the operating table was related to the risk of complication, particularly infections complications [16]. In this study, the number of wound infections in the control group more than honey group, but not statistically significant.

We assessed the insulin resistance by the HOMA-IR method. Although the hyperinsulinemic euglycemic clamp is the gold standard for evaluating insulin resistance, HOMA-IR is commonly used and is well validated in literature. This method is a relatively non-invasive and convenient way to estimate insulin sensitivity and glucose concentrations [17]. Moreover, it has been shown in previous studies that the HOMA-IR model can be utilized as a reliable indicator and marker of postoperative insulin resistance in surgical patients [13].

In this study, 50 ml of honey is equivalent to 70 grams of honey. In each of 100 grams of honey, contained approximately 38 grams of fructose and 31 grams of glucose. In the process of digestion after honey intake the principal carbohydrates fructose and glucose are quickly transported into the blood and can be utilized for energy requirements by the human body [18]. Honey is lower glycemic index than sugar. Research has shown that foods with a low glycemic index allow for only a small increase in blood glucose [19].

A possible criticism of this study is the small number of patients. However we performed sample calculation aiming for a power analysis above 80%. Some other trials having insulin resistance as the primary endpoint have also randomized fewer than 15 subjects in each arm of the study. If a difference in treatment can be seen with a small sample (but with sufficient power analysis), adding subjects may only

increase duration and cost of the study. We believe that samples should be large enough to detect possible differences reasonable enough to be feasible and small enough to detect efficient therapies. Another criticism is that we did not observe any intraoperative confounding factors, that could have impact on the result. However we excluded patients with any non-compliance with the study protocol, or presented significant intraoperative occurrences, or experienced prolonged operations (lasting more than 4 hours) and only elicited in the study patients with ASA score I and II.

5. CONCLUSION

In conclusion, compared to conventional overnight fasting, preoperative consumption of honey drink suppressed perioperative insulin resistance without causing adverse effects. In addition, the honey drink appears to increase patient well-being, by reducing thirsty, hungry and tiredness in patients undergoing elective open colorectal surgery.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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