Pre-Operative Intravenous Co-Administration of Ranitidine and Metoclopramide: Effect on Gastric Content in Laparoscopic Cholecystectomy

KHALDA G. RADWAN, M.D.*; SOHAILA H. OMAR, M.D.*; MAHA A. YOUSSEF, M.D.*;
HANAN FAROUK, M.D.*; NABAWEYA M. KAMAL, M.D.* and ABDEL NASSER A. SABRA, M.D.**
The Departments of Anesthesiology* and Pharmacology** Theodor Bilharz Research Institute.

Abstract

Objective: This prospective, randomized, double-blind study was performed to evaluate the effects of intravenous co-administration of metoclopramide and ranitidine on pre-operative gastric contents in patients receiving general anesthesia for elective laparoscopic cholecystectomy surgery, a procedure with high risk of aspiration.

Material and Methods: Eighty ASA physical status I-II consenting patients were randomly assigned to receive, intravenously 5ml of either saline to control Group C, 50mg ranitidine to Group R, 10mg metoclopramide to Group M and finally combined ranitidine and metoclopramide to Group RM, fifteen minutes before the induction of anesthesia. Each group includes 20 patients. Before surgery and after induction of anesthesia a 14-F multiorifice nasogastric tube was inserted to aspirate the gastric contents of all patients. The volume and pH of collected gastric fluid were estimated.

Results: Data revealed that pH, in both ranitidine alone group (R) and in combination with metoclopramide group (MR) were significantly higher than control (C) and metoclopramide (M) groups (p<0.01). Data also revealed that collected gastric fluid volumes were significantly lower in metoclopramide alone and in co-admixture with ranitidine groups (M and RM) (p<0.01) when compared with control and ranitidine groups (C and R), and were also significantly lower in group RM when compared with M (p<0.01).

Conclusion: Intravenous prophylactic ranitidine and metoclopramide co-administration, may be an easy and useful method to decrease the volume while increasing the pH of gastric contents, and therefore may reduce the number of patients at risk for aspiration pneumonitis in laparoscopic cholecystectomy procedures.

Key Words: Laparoscopy – Metoclopramide – Preoperative gastric content – Ranitidine.

Introduction

STRESS delays gastric emptying even in healthy and not "full stomach" surgical patients [1]. There is evidence of an increased risk of aspiration in surgical patients if the volume of the gastric contents is greater than 25ml and the pH is less than 2.5 [2]. However, Olsson et al. [3] stated that routine prophylaxis for aspiration was no longer recommended in patients not in apparent risk. Nevertheless, a reduced level of consciousness interferes with the protective upper airway reflexes and is also associated with impaired function of the lower esophageal sphincter [4,5] and increased risk of pulmonary aspiration especially in patients who were operated upon in the supine position [6]. Therefore patients undergoing laparoscopic surgery using abdominal gas insufflations may be at risk for acid aspiration syndrome. Published reports about the effect of intravenous pharmacotherapy on preoperative gastric contents in these patients are scarce.

Many drugs, including histamine-2 (H2) receptor antagonists (e.g., cimetidine, ranitidine, and nizatidine), prokinetics and proton pump inhibitors such as metoclopramide and omeprazole, and antacids such as sodium bicarbonate, calcium carbonate, aluminum and magnesium compounds have been used in an attempt to eliminate the risk of pulmonary aspiration by decreasing the acidity and volume of the gastric fluid [1-3]. H2 receptor antagonists inhibit secretion of gastric acid. They bind competitively to receptors on the basal parietal cell membrane, decreasing both the pH and volume of gastric contents [3,7]. Metoclopramide, a dopamine antagonist and the most common prokinetic drug, stimulates esophageal, gastric, and small
bowel activities. Its combination with an H$_2$ receptor blocker has been advocated to decrease post-operative emesis and to reduce the risk of aspiration pneumonitis [2,8].

As drugs given preoperatively by the oral route might alter the volume or pH of gastric contents in fasting patients we therefore, designed this prospective randomized, double-blind investigation to evaluate the effects of prophylactic intravenous metoclopramide and ranitidine co-administration, on preoperative gastric contents in patients receiving general anesthesia for laparoscopic cholecystectomy.

**Material and Methods**

This study was done in Theodor Bilharz Research institute after obtaining institutional ethical committee approval and patient’s written informed consents from each patient scheduled for the study. Eighty adult patients (aged 21-5yr, ASA physical status I or II) undergoing elective laparoscopic cholecystectomy were included in this randomized, double-blind, controlled clinical trial. Obese (>20% of ideal body weight), diabetic patients, those with a history of any gastrointestinal disorder, who were receiving any medication known to interfere with gastrointestinal function and affect gastric fluid composition or gastric emptying were excluded.

The patients were allocated according to a computer-generated randomization method to one of four groups (n= 20 each). Fifteen minutes before the induction of anesthesia, 5mL was given intravenously (IV) in the form of either saline to Control Group C, 50mg ranitidine (Zantac, GlaxoSmithKline, Italy) to Group R, 10mg metoclopramide (Primperan, Sanofi, Aventis, Egypt) to Group M and finally combined ranitidine and metoclopramide to Group RM. Saline was added to all solutions to reach the same volume (5mL), by an anesthesia assistant who did not know the contents of the IV injection.

All patients fasted after midnight, and no other premedication was given. The fasting blood sugar was measured before induction using a blood glucose meter (SureStep, Lifescan inc. Milpitas, California, USA) in order to exclude hypoglycemia. Anesthetic monitoring as regard five leads electrocardiography, non invasive blood pressure, pulse oximetry, capnography, anesthetic gas analyzer, temperature and peripheral nerve stimulator (Infinity Kappa, Dräger, Lübeck, Germany) was applied to all patients in different groups. Anesthetic induction was performed with fentanyl $1 \text{µg kg}^{-1}$ IV, propofol $2 \text{mg kg}^{-1}$ IV, and tracheal intubation was facilitated with atracurium $0.5 \text{mg kg}^{-1}$ IV. The lungs were ventilated, taking care to avoid inflation of the stomach. Anesthesia was maintained with isoflurane to keep the end-tidal anesthetic concentrations within 0.8-1.2% in 50% oxygen/air mixture. Muscle relaxation was maintained with 0.1mg kg$^{-1}$ atracurium IV guided by peripheral nerve stimulator.

After tracheal intubation and before start of surgery, an anesthesiologist who did not know which drug was given to the patient inserted a 14-Fr multiorifice nasogastric tube (NGT) (Japan Sherwood, Tokyo, Japan) into the stomach. Its placement within the stomach was verified by auscultation over the epigastrium during the introduction of 10ml of air. Gastric fluid samples were obtained by gentle aspiration with a 50ml syringe by an investigator who was unaware of the patient’s pre-anesthetic medication. Aspirations were attempted with the patient held in supine, reverse Trendlenburg, and lateral positions to maximize gastric emptying. At any position, pressure was applied over the epigastrium, and gastric contents were aspirated intermittently during removal of NGT. The volume of gastric contents was measured with a syringe. The time taken for gastric aspiration in each patient did not exceed 10 minutes. Another NGT was inserted till end of the procedure. Great care was taken to avoid epistaxis, vomiting, oxygen desaturation or any other serious complications during insertion of NGT. The duration of all surgeries was within two hours. The pH of the gastric fluid was determined immediately using a pH meter (Horiba F-8L, Horiba, Kyoto, Japan). The control group received both H$_2$ antagonist and anti-emetic after the study time to guard against post-operative nausea and vomiting (10 min post-induction) in such vulnerable patients.

**Statistical analysis:**

A power analysis was performed to determine sufficient sample sizes required for establishing significant differences in the gastric variables based on the results of the preliminary study using an $\alpha$ value of 0.05 and power of 0.9, a sample of 20 patients in each group was required. Results are expressed as mean ± standard deviation or number (%). Comparison between numerical data was performed using one way analysis of variance (ANOVA) with post-hoc Kruskal-Wallis test. Comparison between categorical data was performed using Chi square test. The data were considered significant if $p$ values was $\leq 0.05$ and highly significant if $p<0.01$. Statistical analysis was performed with the aid of the SPSS computer program (version 12 windows).
Mean value

**Results**

All inductions of anesthesia were uneventful, and no patients had coughing, laryngospasm or vomiting during the induction. Patient's Demographic data, ASA status ratio, and duration of surgery were comparable in all groups (Table 1). Data revealed that pH in both groups R and MR was significantly higher compared with both C and M groups (\(p<0.01\)) (Fig. 1). On the other hand, collected gastric fluid volumes were significantly lower in M and RM groups when compared with C and R groups (\(p<0.01\)), and were also significantly lower in group RM when compared with group M (\(p<0.01\)) (Fig. 1). Fasting hours and preoperative blood glucose level were comparable among groups (Table 2). More patients were considered at high-risk for aspiration in the control group (gastric fluid volumes >25mL [40%], and pH <2.5 [65%]) than all other groups, while in M group 70% had pH below 2.5 and 45% in R group had volume more than 25mL. No patients in combined group RM experienced low pH or high volume (Table 2).

**Discussion**

Intravenous ranitidine in combination with metoclopramide, co-administered 15 minutes before surgery significantly reduced risk factors for aspiration, in the current study, by raising pH of gastric fluid, and also by reducing its volume.

The co-admixture was superior to metoclopramide and comparable with ranitidine, in terms of gastric pH, when either drug is administered as the sole agent. It was also superior to ranitidine and metoclopramide, in terms of volume of collected gastric fluid, when either drug is given as the sole agent.

Although published studies on the combination of ranitidine and metoclopramide on gastric content
is scarce, yet data from current study are in accordance with another previous trial, on outpatients receiving intravenous anesthesia for laparoscopic gynecologic surgeries [2]. Another study [9] claimed that metoclopramide, which decreases gastric volume due to a gastrokinetic action and has antiemetic effects, is used most effectively when combined with H2-receptor antagonists, to decrease the risk of aspiration [9,10].

Other previous studies have failed to demonstrate a significant advantage of this drug combination over an H2 receptor antagonist alone. However, this may be attributed to involvement only of the morbidly obese population in such study [11]. However, metoclopramide may offer an additional protective effect as a result of its ability to increase lower esophageal sphincter tone [2].

Patients will be at risk of aspiration if the stomach is not empty, patients with diabetes mellitus, increased intracranial pressure, hiatus hernia, gastrointestinal obstruction, recurrent regurgitation, and dyspeptic symptoms known to delay gastric emptying. Gastric emptying may also be delayed in patients who have previously undergone upper gastrointestinal surgery, in those recently injured or receiving opioids, and in women in labour. Morbidly obese patients may be at risk, because the intra-abdominal pressure is higher and the incidence of hiatus hernia is greater than in non-obese patients [12,13].

The current study was designed to be performed on laparoscopic cholecystectomy patients, as these patients are proven to be at a higher risk of aspiration [14]. Generally, patients who are undergoing upper abdominal surgery should be considered at risk, as surgical manipulation may push gastric contents back up to the mouth. Moreover, patients who are undergoing laparoscopic surgery are at a higher risk of aspiration, because of the increase in intra-abdominal pressure and lithotomy or the head-down position that may encourage residual gastric contents to regurgitate, as well as increase in secretion of gastric acid. Also, these patients may regurgitate or vomit bile-stained fluid [15]. In fact, pulmonary aspiration has been reported in patients undergoing laparoscopic cholecystectomy [14]. The high incidence of regurgitation after laparoscopic cholecystectomy comes as no surprise even when patients are fasting and in spite of all the measures taken, where an orogastric tube is introduced at induction of anesthesia and during surgery, to empty the gas from the stomach. This risk is due to the presence of pockets within the stomach far from reach of the tip of the gastric tube [16].

If general anaesthesia is not sufficiently deep, and also during emergence with early removal of an airway before the patient spontaneously regains consciousness, airway reflexes (such as coughing, hiccoughs, or laryngospasm) or gastrointestinal motor responses (such as gagging or recurrent swallowing) may be evoked. These reflexes may be associated with distension of the stomach, regurgitation and vomiting, increasing the risk of pulmonary aspiration [17,18].

During intermittent positive pressure ventilation, anesthetic gas may be insufflated into the stomach and may increase the risk of regurgitation, particularly when high pulmonary inflation pressures are required. There has been ongoing concern that avoidance of the use of a cuffed tracheal tube might increase the incidence of pulmonary aspiration [19]. Nevertheless, a cuffed tracheal tube may not effectively prevent leakage of fluid into the lower airway [20]. Moreover, incidence of regurgitation may be increased as surgery gets longer, as long as 2h [20].

Even if the patient is fasted, the stomach is often not totally empty. On average about 25ml of acidic gastric juice remains in the stomach, but this can be as much as 200ml [21]. Traditionally, the patient has been said to be at risk when the volume of gastric acid is greater than 25ml (or 0.4ml kg−1) and the pH less than 2.5 [22] but if these cut-off values are applied, roughly 50% of fasted patients can be regarded as at increased risk of aspiration. Even if the stomach is empty, vomitus may come from the small intestine. Aspiration of gastric acid damages lung tissue, and the extent of the damage increases proportionally as acidity and volume increase. Bile damages the lungs more severely than gastric acid [15,23]. Greater precaution is required if there is a risk of aspiration of bile. All these general and specific issues place patients scheduled for laparoscopic surgery under a higher risk of aspiration pneumonitis and lung damage.

Prophylactic medications are administered based on their ability to increase gastric pH or decrease gastric volume 24. Histamine 2 antagonists (e.g., ranitidine) increase gastric pH. They bind competitively to receptors on the basal parietal cell membrane, and are often administered to patients who are at high risk for aspiration [9,23]. Bowes et al. [24], proved that a single 300mg dose of ranitidine given orally 2-3h before magnetic
resonance cholangiopancreatography could reduce the signal from the stomach and duodenum, and thus increase the conspicuousness of the biliary tree.

Metoclopramide is prescribed for patients at risk for aspiration, because it increases low esophageal sphincter tone, facilitates gastric emptying, and has an antiemetic effect. This medication works both centrally and peripherally as a dopaminergic antagonist [23].

Laparoscopic cholecystectomy patients, especially the obese female population, typically receive pharmacotherapy in our hospital, either ranitidine 50mg IV or metoclopramide 10mg IV, although routine administration of these drugs has not been recommended by the ASA [25]. However, recent guidelines by the ASA recommend routine preoperative use of gastric acid secretion blockers for patients who have apparent increased risk of aspiration. There is no sufficient evidence published to evaluate whether reduced gastric acid secretion is associated with decreased morbidity and mortality. Additional trials are needed to prove their efficacy in decreasing the frequency of pulmonary aspiration.

A limitation of the study may be directed toward the fact that the gastric volumes in this study are not representative of the total volume of gastric contents, because emptying the stomach with a nasogastric tube has not been shown to ensure complete emptying of gastric contents. Hence, it is possible that gastric volumes might have been underestimated. Dye absorption technique and fiberoptic gastroscopy are more reliable than blind aspiration, but they are more complicated, time consuming, and clinically limiting [2].

In conclusion, prophylactic intravenous co-administration of ranitidine and metoclopramide may be an easy and useful method to decrease the volume and increase the pH of gastric contents. Accordingly, this can reduce the risk of aspiration pneumonitis, in patients scheduled for laparoscopic cholecystectomy, which is a procedure known to place these patients in a higher degree of risk of aspiration pneumonitis, thus, targeting a safe patient outcome for such patients.

References


