Effects of intravenous ranitidine and esomeprazole on gastric pH and volume in patients undergoing emergency appendicectomy

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ABSTRACT

Introduction: Pulmonary aspiration of gastric contents is a potentially life threatening complication of general anaesthesia especially in high risk patients undergoing emergency anaesthesia. Classically, ranitidine has been used to reduce gastric pH and volume. Esomeprazole, the S-isomer of omeprazole, is a newer generation proton pump inhibitor whose effect on gastric pH and volume in emergency surgeries has not been determined. **Materials and Methods:** This was a prospective, randomised, double blind study to compare the effect of intravenous esomeprazole and ranitidine on gastric pH and volume in patients undergoing emergency appendicectomy. Following induction of anaesthesia, seventy patients of American Society of Anesthesiologists physical status I or II had their gastric contents aspirated via a nasogastric tube. They were then randomised to receive either intravenous esomeprazole 40 mg or intravenous ranitidine 50 mg. A second aspiration of gastric contents was done three hours later. The pH and volume of gastric contents of both aspirations were recorded. **Results:** Both intravenous esomeprazole and ranitidine significantly reduced the gastric fluid acidity (p=0.001) and volume (p=0.001). There were no significant differences measured between the two groups in terms of gastric fluid pH (p=0.86) and gastric fluid volume (p=0.14) after administration of study drugs. **Conclusion:** Esomeprazole and ranitidine given intravenously were both comparable in reducing the volume and acidity of gastric secretions in patients undergoing emergency appendicectomy.

Keywords: Appendicectomy, esomeprazole, acid suppression therapy, pulmonary aspiration, ranitidine

INTRODUCTION

Aspiration of gastric contents is a potentially life-threatening complication that can arise during general anaesthesia, especially in high risk patients undergoing emergency surgery. [1-3] The overall incidence of perioperative pulmonary aspiration is 1:7103 in the general surgical population, but a higher incidence of

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1 : 4,474 occurs amongst patients undergoing emergency surgery. [4] Aspiration of gastric contents into the lungs can lead to pneumonitis/pneumonia or acute lung injury which may progress to adult respiratory distress syndrome (ARDS) requiring mechanical ventilation, or even death (1 : 99,441). [4]

The severity of clinical presentation and progression of complications depend on the acidity (pH) and volume of the aspirated gastric fluid as well as the presence of food particles in the aspirate. [5] The combination of these critical factors in causing aspiration pneumonitis were alluded to by Roberts and Shirley, [6] and Teabeaut. [7] In a study performed on rhesus monkeys, Roberts and Shirley identified a gastric fluid volume of more than 25 ml (0.4 ml/kg) as a risk factor [6] whereas Teabeaut's experiments on rabbits discovered that a gastric pH of less than 2.5 and the presence of food particles in the aspirate led to aspiration pneumonitis.[7] Results of such animal experiments have been extrapolated to the human population as it is unethical to carry out similar studies on humans. Thus, a critical gastric pH of less than 2.5 and gastric fluid volume of more than 25 ml have been quoted as risk factors that increase the likelihood of aspiration pneumonitis. [2, 6, 7]

Various pharmacological agents have been proven to successfully modify gastric volume and/or acidity. Non-particulate antacids e.g. sodium citrate; prokinetics e.g. metoclopramide, and histamine-2 (H_2) receptor antagonists (H_2RA) e.g. ranitidine, famotidine have been used as prophylaxis against acid aspiration in high risk patients undergoing elective or emergency surgeries. [8] H_2RA competitively inhibits the histamine binding to H_2 receptors, thereby reducing gastric acid output and raising the gastric pH. On the other hand, proton pump inhibitors (PPIs) bind to the proton pump of parietal cells in the gastric mucosa inhibiting the secretion of hydrogen ions and hence reduces gastric secretion output and acidity. [9, 10] As compared to H_2RA, PPIs act on the final common pathway of the stimulatory process of acid secretion.

Esomeprazole is the S-isomer of omeprazole. The S and R isomers of omeprazole are equally effective as acid secretion suppressors. However, the efficacy of esomeprazole is increased as the result of esomeprazole's slower metabolism, allowing prolonged availability at the proton pump leading to longer duration of action of up to 24 hours. The oral preparation of esomeprazole has an onset of action at 30-60 minutes while the intravenous (IV) preparation has an onset of action at 15-30 minutes. In contrast, oral ranitidine begins its action within two hours while the IV preparation acts within 30-60 minutes. The peak plasma level of esomeprazole is achieved within 1.5 hours as compared to ranitidine which takes 2-3 hours. [9, 10]

The use of proton pump inhibitors as acid aspiration prophylaxis in elective or emergency surgery to modify the pH and to reduce the gastric secretion is uncommon as compared to the use of IV ranitidine. There are currently limited data on the effectiveness of IV esomeprazole on perioperative gastric fluid pH and volume. This study was conducted to compare the effectiveness between IV esomeprazole and IV ranitidine in modifying the gastric fluid properties in patients undergoing emergency appendicectomy.

MATERIALS AND METHODS

This was a prospective, randomised, double blind clinical study. After obtaining institutional ethics committee approval and patients' informed consent, seventy patients with American Society of Anesthesiologist (ASA) physical status I or II patients, aged between 18-65 years scheduled for emergency appendicectomy (open or laparoscopic) were recruited. Those excluded were obese patients (body mass index = BMI >28 kg/m²), patients with oesophageal and gastric disorders and those taking medications that may have altered gastric motility and secretion. Also excluded were patients with a past or present history of drug or alcohol abuse, females who were pregnant or lactating and where suxamethonium was contraindicated. The recruited patients were allocated using computer generated randomised numbers to one of two groups. Patients in Group R received IV ranitidine whereas patients in Group E received IV esomeprazole.

Patients were fasted for at least 6 hours prior to surgery. In the operating room, IV access was established and standard monitoring devices e.g. electrocardiograph, non-invasive blood pressure, pulse oximeter and capnograph (once intubated) were applied. After pre-oxygenation, rapid sequence induction with cricoid pressure application was performed after induction with IV sodium thiopentone 4 mg/kg and suxamethonium 1.5 mg/kg, followed by endotracheal intubation. Anaesthesia was maintained with oxygen, air and sevoflurane to achieve a minimum alveolar concentration of 1.2. Muscle relaxation was continued either with atracurium 0.3 mg/kg or rocuronium 0.6 mg/kg. A 12 or 14 FG nasogastric tube was inserted and correct placement was ascertained by positive auscultation over the epigastrium with injection of 10 ml of air. The gastric fluid samples were obtained as much as possible using a 10 ml syringe by an investigator who was blinded to the study drug given. Aspiration was attempted with the patient in supine and reverse Trendelenburg positions. The nasogastric tube was repositioned several times to maximise gastric emptying before surgery started. The first sample of gastric fluid was aspirated after tracheal intubation and insertion of the nasogastric tube and the second sample was taken three hours later. The pH and volume of both aspirates were measured. The study drugs (diluted to 3 ml with normal saline) were administered following the first sampling. Patients in Group R received IV ranitidine 50 mg whereas patients in Group E received IV esomeprazole 40 mg. Both were given as a slow bolus over 5 minutes. The volume of gastric fluid was measured using a 10 ml syringe while its pH was determined using a portable pH meter, DIGITRAPPER MK III (Synectics Medical, U.S.A), which has an accuracy of ± 0.1 pH units. Once the second sample had been collected, the nasogastric tube was removed. Adverse effects related to the study drugs such as hypotension, arrhythmias, hypersensitive reactions, pruritus, confusion and hallucination were also monitored.

The power of the study was determined at 80% and α value at 0.05. Assuming a drop-out rate of 5%, a total of 70 patients were included in this study. Statistical analysis within groups was performed using the Wilcoxon test and between groups using the Mann Whitney U test. Demographic data and method of surgery were analysed using the

Table 1: Comparisons of the demographics between groups.

	Group R (n=35)	Group E (n=35)	*p* values
Age (years) ± SD	29.0 ± 11.1	28.0 ± 9.9	0.88
Gender : Male / Female	22/13	19/16	0.47
Race : Malay / Indian / Chinese / Others	20/5/7/3	22/3/7/3	0.90
ASA: I / II	29/6	27/8	0.55
Weight (kg)	64.1 ± 10.0	61.5 ± 8.3	0.29
Height (m)	1.6 ± 0.1	1.6 ± 0.1	0.77
Method of surgery : Open / Laparoscopic	15/20	9/26	0.13

ASA: American Society of Anesthesiologist

Student t test. A p value of < 0.05 was considered statistically significant.

RESULTS

The demographic data and method of surgery are presented in Table 1. There were no significant differences with regards to age, gender, race, ASA status, weight, height and method of surgery.

Table 2 presents the median (25-75th percentile) gastric pH and gastric volume at pre-administration and post-administration of the study drugs. The data was not normally distributed. Both IV esomeprazole and ranitidine significantly reduced the gastric pH (p=0.001) and volume (p=0.001) three hours after administration. No significant differences were measured between the two groups in terms of post-administration gastric pH (p=0.86) and post-administration gastric volume (p=0.14).

No adverse effects related to the study drugs were observed.

DISCUSSION

Studies comparing ranitidine with various proton pump inhibitors (PPIs) have reported varying outcomes. Several studies have demonstrated that ranitidine significantly reduces gastric pH and volume in comparison to some PPIs, while other studies have found both drugs to be equally effective. [11-14] These differences in findings could be attributed to the different routes of drug administration, dosing frequency, timing of drug administration and the study group population. [11-14] To date there have not been any studies comparing IV esomeprazole with ranitidine, especially in emergency anaesthesia. Therefore, we compare with studies that had looked at

Table 2: Comparisons of gastric pH and volume between the two groups.

		Pre-administration	Post-administration	*p* values
pH of gastric contents	Group R	1.4 (1.2-1.8)	3.0 (2.0-5.0)*	0.001
	Group E	1.3 (1.1-1.4)	3.6 (2.3-4.7)*	0.001
Volume of gastric contents (ml)	Group R	8.0 (5.0-15.0)	2.0 (2.0-3.0)#	0.001
	Group E	5.0 (4.0-12.0)	(1.5-2.0)#	0.001

pantoprazole and ranitidine instead.

Memiş *et al.* and Goel *et al.*, in comparing ranitidine with pantroprazole given Intravenously before induction of anaesthesia for elective surgery, did not find any significant difference between the two drugs in reducing gastric pH and volume. [11, 12] Although our study population and timing of drug administration was different (emergency appendicectomies, drugs given intravenously post induction of anaesthesia), we also did not detect any significant difference between rantidine and esomeprazole in reducing gastric pH or volume. Meanwhile, Sadarwarte *et al.* compared IV pantoprazole with IV esomeprazole and discovered both drugs to be equally effective in reducing gastric volume, however the latter was more effective in reducing gastric pH. [13] It is therefore interesting that we found intravenous ranitidine to be as effective as intravenous esomeprazole in reducing gastric pH and volume. Hence, when cost is taken into consideration, ranitidine may be a preferred drug.

The risks of aspiration pneumonitis in elective surgery are low thus practice guidelines do not recommend the use of preemptive pharmacologic intervention in healthy patients.[4,15,16] The risk of aspiration pneumonitis is higher in emergency surgery,[4,16] but in emergency appendicectomy per se it is acceptably low (about 6%),[16-18] thus allowing us to study this population without undue risks. This is supported by our study results which showed a low pre-existing gastric volume (< 25 ml) in the stomach after fasting for at least 6 hours despite the pH being less than 2.5.

The combination of gastric pH less than 2.5 and volume of more than 25 ml (>0.4 ml/kg) are often quoted as the critical factors for aspiration pneumonitis. [1-3, 5-7] When both of these variables were evaluated together, none of the patients from both groups had this combined risk. However, 25% patients in Group E and 28 % patients in Group R had a pH of less than 2.5 despite receiving the study drugs (p =0.73). Further studies are required to evaluate if higher esomeprazole dosages may significantly alter gastric pH and/or volume in comparison to ranitidine.

Sixty-six percent of patients in this study underwent laparoscopic appendicectomy. Patients undergoing laparoscopic surgery are at higher risk of delayed gastric emptying and aspiration compared to open surgery due to the increase in intra-abdominal pressure intraoperatively as a result of pneumoperitoneum. [19, 20] The Trendelenburg position adopted for laparoscopic appendicectomy can also lead to the possibility of displacement of residual gastric contents towards the esophagus. [21, 22] These factors may predispose patients to aspiration and may lead to inaccurate collection of gastric contents at 3 hours post-administration of the study drugs. Another factor that could have contributed to inaccurate sampling was our blind aspiration technique via the nasogastric tube to collect the gastric secretions. Despite the various positioning methods used in our study, these manoeuvres may still incompletely empty the stomach and therefore underestimate the gastric fluid volume. There are alternative methods of obtaining gastric aspiration including the use of visually guided gastroscopies and dye dilution techniques. Visually aid-

ed gastroscope sample collection has been found to yield as much gastric content as with blind aspiration. [23] Comparatively, Taylor *et al.*, in their study, showed that gastroscope sample collection was more accurate. [24] However, its use is usually limited to the endoscopic suites and requires technical skills in handling the scope. Estimation by dye dilution has been shown to be similar to blind aspiration though it is more complicated in technique and time consuming. [25] Another limitation of our study is that we did not have a placebo group to ascertain the effectiveness of each drug individually. Therefore, we were unable to truly evaluate the effects of ranitidine and esomeprazole separately on gastric pH and volume.

Our study method was different from other previously reported. First, it was conducted on patients diagnosed with appendicitis scheduled for emergency surgery (appendicectomy) while other studies were of healthy volunteers or those undergoing elective surgery. [11-14] We chose this study population to evaluate the effects of the study drugs in such increased risk patients. Secondly, in our investigation, by administering the study drugs intravenously only after induction and aspiration of preexisting gastric contents. WE made certain that the gastric fluid volume and acidity collected at the second sampling was indeed due to the effects of the study drugs.

In conclusion, esomeprazole 40 mg and ranitidine 50 mg given intravenously were both equally effective in altering gastric secretion properties in patients undergoing emergency appendicectomy.

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