Esomeprazole as a prophylactic agent for acid aspiration syndrome in adult patients undergoing elective surgery: A triple blind placebo controlled clinical trial

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ABSTRACT

Background: To explore the effect of single oral dose of esomeprazole 20 mg, administered a night before surgery, on intragastric pH and volume in adult patients undergoing elective surgery by excluding cases contaminated with duodenogastric refluxate.

Patients and Methods: This prospective, triple blind, randomised and placebo controlled clinical trial was conducted to explore the effect of single oral dose of esomeprazole 20 mg, administered a night before surgery, on intragastric pH and volume on 120 adult inpatients of either sex, American Society of Anaesthesiologist physical status I-II, and aged 15–70 years. The patients in Group C (control) received placebo while Group E (Esomeprazole) received esomeprazole orally at 9.00 pm, the night before elective surgery.

On the day of surgery, the gastric contents were aspirated with a large bore, multi-orifice gastric tube passed through an endotracheal tube placed blindly in the oesophagus after tracheal intubation and analysed for pH, volume and the presence of bile salts.

Results: Thirty nine samples (33%) out of 117 were contaminated with duodenal contents. Duodenogastric reflux significantly affected pH and volume in Group C (p value 0.0003 and 0.0016) and E (p value 0.0401 and < 0.0001). Esomeprazole, after excluding samples contaminated with duodenal fluid, significantly increased pH (p <0.0001), decreased volume (p 0.0068) and the percentage of the patients (2.56% versus 30.76%) considered "at risk" compared with placebo (p 0.0015) according to the criteria defined (pH ≤ 2.5 and volume ≥ 25 ml).

Conclusion: Esomeprazole 20 mg administered orally a night before elective surgery improved the gastric environment (pH < 2.5 and volume > 25 ml/kg) at the time of induction of anaesthesia excluding samples contaminated with duodenogastric reflux.

Introduction

Duodenogastric reflux is the retrograde flow of duodenal contents into the stomach that then mixes with acid and pepsin.[1] Huges et al[2] reported 33%, Raved et al[3] 8.98 % and Wolverson et al[4] 46% incidence of duodenogastric reflux in healthy subjects. Our first aim was to determine whether or not duodenogastric reflux significantly affects gastric pH and volume.

Esomeprazole, a proton pump inhibitor, is used in peptic ulcers and other acid dyspeptic disorders of the upper gastrointestinal tract in a dose of 20 mg orally once daily.[5] The effect of a single oral dose of esomeprazole 20 mg on preoperative gastric fluid pH and volume has not yet been studied. The second aim of this study was to determine whether or not a single oral dose of esomeprazole 20 mg, administered a night before surgery, is effective in increasing the pH ≥ 2.5 and decreasing volume ≤ 0.4 ml/kg or 25 ml in adult patients undergoing elective surgery by excluding those cases contaminated with duodenogastric reflux, if duodenogastric reflux significantly affects pH and volume of gastric contents.

Patients and methods

The protocol of the study was approved by the Research and Ethics Committee and written, informed patient consent was obtained. One hundred and twenty patients (120) of American Society of Anaesthesiologists (ASA) physical status I-II, aged 15–70 years scheduled for elective surgery under general anaesthesia participated in the study.

We excluded patients from our study known to have upper gastrointestinal disorders, the morbidly obese having a body mass index (BMI) of more than 40 kg/m^2, those receiving medications known to affect the secretory and/or motor functions of the stomach, difficult intubation, i.e. Mallampati class IV and/or mouth opening less than 5 centimetres and/or a thyromental distance less than 6.5 centimetres and/or history of documented difficult intubation, intestinal obstruction, parturients and Diabetes

Mellitus. Patients who took the study drugs but their gastric aspirates showed bile acids due to duodenogastric reflux were not included in the final statistical analysis while analysing pH and volume of gastric contents. We did not consider these samples as true gastric contents because in these samples alkaline duodenal fluid was mixed with acidic gastric contents.

The patients were randomly allocated by sealed envelope method to receive either esomeprazole 20 mg (n = 60) or placebo (n = 60) by oral route at 9.00 pm on the night before surgery. All patients also received oral diazepam 10 mg at the same time. On the pre-operative anaesthesia visit, the nature and purpose of the study was explained to all patients. According to the hospital policy, all patients were fasted from 12 midnight irrespective of the nature (solids or liquids) of the last meal taken. Age, sex, weight, height, BMI, ASA physical status, and the drug given were recorded for each patient. Before the start of anaesthesia, all patients were asked if they had been aware of any unusual feelings (side-effects) after taking the medications, the night before surgery.

General anaesthesia was induced with injected fentanyl, propofol, and maintained with sevoflorane and air in oxygen. The lungs were ventilated taking care to avoid inflation of the stomach. Tracheal intubation was facilitated by rocuronium. Another endotracheal tube sized 8.5 mm internal diameter lubricated with paraffin liquid internally was passed in the oesophagus with anterior displacement of the larynx. A predetermined length of orogastric tube (from xiphoid process to ear lobules and from ear lobules to nasal tip)[6] (Jamjoom Medical Industries, Jeddah, Saudi Arabia) sized 16 F was passed through the oesophageally placed endotracheal tube[7] into the stomach.

Placement of the orogastric tube within the stomach was confirmed by auscultation over the epigastrium during introduction of 10–15 ml of air. Gastric fluid samples were collected by gentle aspiration with 60 ml of syringe by an investigator who was unaware of the preanaesthetic medication. Aspirations were attempted while the patients were held in supine and then in left and right lateral positions.[8] The orogastric tube was removed followed by an oesophageally placed endotracheal tube. Any problem faced during inserting or removing the oro-oesophageally placed endotracheal tube or orogastric tube was also recorded. Gastric contents were visually inspected for the presence of blood. The volume of gastric contents was measured with graduated syringe and pH immediately with pH meter (Model 215 version 3.4, Denver Instrument Company, United States). The pH meter was calibrated using standard buffers at pH values of 4.0, 7.0 and 9.20. This pH meter has a precision of 0.01 units over the entire pH range. A minimum of one millilitre volume of gastric contents was sufficient for pH determination with pH meter. Samples less than one millilitre were considered as no gastric contents because a minimum volume of one millilitre of gastric contents was sufficient for pH- metery.

Using bile salts as a marker for bile, we applied the qualitative Hay's Sulphur test for the presence of bile salts. This test depends on the principal that bile salts have the property of reducing the surface tension of fluids in which they are contained.[9] In this test finely powdered sulphur is sprinkled upon the surface of cool (170C or below) liquid. If the sulphur remains floating on the surface, bile salts are absent. On the other hand, if bile salts are present the sulphur sinks down, sooner or later, in accordance with their percentage. If bile salts are present in the fluid from 1:5000 (0.02% or 200µg/ml) to 1:10,000(0.01% or 100µg/ml) sulphur at once begins to sink and is all precipitated in two or three minutes; even in a dilution of 1:120,000 (0.0008 % or 8.33 µg/ml) precipitation occurs.[10]

Time since premedication, time since *Nil per Os* (NPO), pH, volume of gastric contents and the result of the Hay's Sulphur test were also recorded for each patient. On the basis of Hay's Sulphur test, we further divided Group C into Subgroups C-1 and C-2 and Group E into Subgroups E-1 and E-2 to observe

Table I: Physical characteristics of patients and timing of events. (Values are expressed either as mean ±SD or numbers (percentage)

Physical characteristics of patients	**Group C n = 60**	**Group E n = 60**	**p value**
Age (years)	34.78 ± 13.44	34.08 ± 10.25	0.7490
Sex Male Female	 30 (50%) 30 (50%)	 30 (50%) 30 (50%)	1.0000
ASA physical status Class – I Class – II	 49 (81.66%) 11(18.33 %)	 44 (73.33%) 16 (26.66%)	0.3822
Weight (kilograms)	73.68 ± 15.28	78.47 ± 13.92	0.0753
Height (centimetres)	161.31 ± 7.84	163.14 ± 10.63	0.2871
Body Mass Index (kilograms/meter^2)	28.40 ± 5.80	29.58 ± 5.43	0.2524
Timings of events			
Time since premedication (minutes)	832.25 ± 136.51	812.50 ± 132.68	0.4232
Time since NPO (minutes)	661.85 ± 138.03	636.33 ± 131.27	0.3016

Table II: pH and volume of gastric contents. (Values are expressed as mean ± SD)

Variables	Group C n = 60		Group E n = 60	
	Group C-1 n = 59	Group C-2 n = 39	Group E-1 n = 58	Group E-2 n = 39
pH	3.06 ± 1.91	1.90 ± 0.47	4.75 ± 1.86	3.97 ± 1.66
Volume (millilitres)	38.72 ± 33.52	19.60 ± 18.56	29.77 ± 32.98	10.70 ± 7.39

Note: Samples mixed with blood (1 in Subgroup C-1 and 2 in Subgroup E-1 are not included.
Group C-1 and Group E-1 represent contaminated samples with duodenogastric refluxate.
Group C-2 and Group E-2 represent non-contaminated samples.
Comparison between Subgroups
Comparison of pH and volume between Group C-1 and Group C-2 (p value 0.0003 and 0.0016).
Comparison of pH and volume between Group E-1 and Group E-2 (p value 0.0401 and < 0.0001).
Comparison of pH and volume between Group C-2 and Group E-2 (p value <0.0001and 0.0068).

Table III: Patients at risk according to defined criteria. (Values are expressed as numbers (percentage))

Variables	Group C -2 n = 39	Group E -2 n = 39	p value
Patients with pH ≤ 2.5	37 (94.87 %)	11 (28.20 %)	<0.0001
Patients with volume ≥25 ml	12 (30.76 %)	1 (2.56%)	0.0015
Patients with pH ≤ 2.5 and volume ≥25 ml	12 (30.76%)	1 (2.56%)	0.0015

Note: Samples mixed either with duodenal contents (39) or blood (3) are not included.

the impact of duodenogastric refluxate on pH and volume of gastric aspirates.

Statistical analysis was performed using GraphPad Software, Inc, San Diego, United States, and results are expressed as absolute values (percentage) and mean ± standard deviation (SD).

Statistical comparisons between Groups C and E were carried out using two-tailed Student's (unpaired) t test for age, weight, height, BMI, time since premedication, time since NPO, pH and volume. Two-tailed Fisher's exact test was applied for sex, ASA physical status and risk of aspiration according to the criteria defined by Roberts and Shirley11 (pH ≤ 2.5 and volume ≥ 0.4 ml/kg or 25 ml). A p value of less than 0.05 was considered statistically significant.

Results

One hundred and twenty (120) adult inpatients undergoing elective neuro (n = 1), thoracic (n = 8), urology (n = 11), gynaecological (n = 14), orthopaedic (n = 28) and general (n = 58) surgery were enrolled. Physical characteristics of patients and timings of events are shown in Table I.

There was no statistically significant difference between Groups C and E regarding age, weight, height, BMI, duration since premedication and duration since NPO.

We obtained gastric contents of all 120 patients. Three samples (2 in Group C and 1 in Group E) were mixed with blood. Hay's test was performed on 117 samples and was positive in 39 (33%) patients (20 in Group C – 9 males and 10 females and 19 in Group E – 9 males and 10 females). These samples do not represent true gastric contents and, therefore, were considered as contaminated and are not included in *final statistical analysis* while analysing pH and volume of gastric contents.

Duodenogastric refluxate significantly affected the pH and volume of gastric contents in Subgroups C-1 and C-2 (p value 0.0003 and 0.0016) and in Subgroups E-1 and E-2 (p value 0.0401 and < 0.0001) as shown in Table II.
The pH and volume of all the Subgroups C-1, C-2, E-1 and E-2 are also shown in Table II. There was a statistically significant difference between the Subgroups C-2 and E-2 (non-contaminated samples with duodenogastric refluxate) regarding pH (p 0.0118) and volume (p 0.0009) of gastric contents.

The proportion (percentage) of the patients considered "at risk" of significant lung injury should aspiration occur is shown in Table III after excluding samples contaminated with duodenogastric refluxate.

There was a statistically significant difference between the Subgroups C-2 and E-2 (p 0.0015) when both pH and volume were combined according to the criteria defined.

All patients were discharged from the hospital without any problem.

Discussion

Esomeprazole is the last of the five proton pump inhibitors (omeprazole, lansoprazole, pantoprazole and rabeprazole)

available in the market for clinical use. Proton pump inhibitors act by irreversibly blocking the hydrogen/potassium adenosine triphosphatase enzyme system (the H^+/K^+ ATPase, or more commonly just gastric proton pump) of the gastric parietal cell. The proton pump is the terminal stage in gastric acid secretion, being directly responsible for secreting H^+ ions into the gastric lumen, making it an ideal target for inhibiting acid secretion.[5]

Duodenal fluid consists of bile, pancreatic juice and small intestine Brunner's gland secretion. All these secretions are alkaline in nature due to bicarbonate HCO_3 – ions.[12] When alkaline duodenal fluid flows in retrograde fashion, then it mixes with acid and pepsin[1] in the stomach and brings the pH towards less acidity thus affecting pH and volume of gastric contents similar to oral ingestion of sodium citrate.

In this current study, we passed an orogastric tube through an endotracheal tube passed blindly in the oesophagus. We obtained a number of benefits by using this technique. Firstly, under general anaesthesia the swallowing reflex is depressed and in an intubated patient, the oesophagus may be occluded by inflated endotracheal tube cuff and it can interfere with insertion of the orogastric tube. Secondly, this technique avoids finding the upper oesophageally opening and coiling of the tube in the mouth even after successfully passing the distal end of the tube into the stomach. Thirdly, moving of the orogastric tube in and out in different patient positions was very easy, thus causing patients minimal trauma. Lastly, we prevented the entry of pooled saliva into the pharynx during insertion, manipulation or removal of the orogastric tube.

Our two samples were found to be mixed with blood due to gastric mucosal entrapment. Gastric mucosal entrapment occurs particularly when air and fluid have been aspirated and the stomach is collapsed. Gastric mucosa is caught in the side holes of the stomach even with gentle suction. Bleeding may occur and blood can be found in the gastric tube thus giving the pH of blood mixed with gastric contents rather than pure gastric contents.

Blind aspiration via gastric tube is the common technique to aspirate the residual volume of gastric contents. In this present study, total gastric volume may have been underestimated by this method in each patient due to the functional divisions of the stomach into antral and fundal sacs.[13] There is good agreement between gastric fluid volumes aspirated blindly and total volumes determined by fibreoptic gastroscopy (mean underestimation 6 ml (22%); range 0–50ml).[14]

Conclusion

Duodenogastric reflux significantly affected both the pH and volume of gastric contents. Preoperative oral esomeprazole 20 mg administered the night before elective surgery increased the pH > 2.5 and reduced residual gastric content volume < 25 ml, possibly reducing the effects of pulmonary aspiration of gastric contents.

Declaration

We conducted Project No. 05-501 entitled "Effect of single orally administered dose of proton pump inhibitors (omeprazole, esomeprazole, rabeprazole…etc. and/or H_2 -receptor antagonists (ranitidine HCl, nizatidine, famotidine…etc) a night before surgery on the intragastric pH and volume in adult patients undergoing elective surgery." A triple blind placebo controlled clinical trial. This project was approved by the College of Medicine Research and Ethics Committee King Saud University, Riyadh, Saudi Arabia. We studied five (5) proton pump inhibitors (omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole) and four (4) H_2 - receptors antagonists (ranitidine, famotidine, nizatidine and cimetidine) with one design, aim and research methodology.

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