ROLE OF ORAL PANTOPRAZOLE AS PRE OPERATIVE PREANAESTHETIC PREMEDICATION FOR THE PROPHYLAXIS OF ACID ASPIRATION IN ELECTIVE ADULT SURGERY

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Background: The effect of drugs affecting gastric *p*H and volume has been studied extensively but the effect of duodenogastric reflux on gastric *p*H and volume at the same time has not been evaluated. **Patients and Methods:** This prospective, triple blind, randomized and placebo controlled clinical trial was conducted on 108 adult inpatients of American Society of Anaesthesiologist physical status I–II, and aged 15–70 years. The patients in Group C (control) received placebo while Group P (Pantoprazole) orally at 9:00 PM, a night before elective surgery. On the next day, gastric contents were aspirated with a large bore, multi-orifices gastric tube passed through an endotracheal tube placed blindly in oesophagus after tracheal intubation and analysed for *p*H, volume and the presence of bile salts. **Results**: Thirty (28.57%) samples out of 105 were contaminated with duodenal contents and 2 with blood. Duodenogastric reflux significantly affected *p*H and volume of gastric contents in subgroups (C-1 versus C-2: *p*-value for *p*H (0.0009) and volume (0.0236) and P-1 versus P-2: *p*-value for *p*H (0.0348) and volume (0.0003). Pantoprazole, after excluding samples contaminated with duodenogastric refluxate, increased pH (p 0.0118), decreased volume (p 0.0009) and the proportion of the patients (p 0.0324) considered" at risk" compared with Placebo. **Conclusion**: Preoperative oral administration of Pantoprazole 40 mg reduced residual gastric content volume ≤25 ml and increased pH ≥2.5, possibly reducing the effects of pulmonary aspiration of gastric contents.

Keywords: Aspiration, duodenogastric refluxate, gastric *p*H, volume, Pantoprazole

INTRODUCTION

Aspiration has been defined as 'inhalation of material into the airway below the level of the true vocal cords'. The severity of aspiration pneumonitis depends upon *p*H and volume of gastric juice aspirated.[1] Acid-suppressing agents are used in the perioperative setting to reduce the risk of lung injury from aspiration of gastric contents. Acid-induced lung injury is associated with a high mortality—approximately 40–50%.[2] Although risk factors for acid aspiration continue to be debated, the literature suggests that patients with a gastric *p*H of <2.5 and a volume of at least 25 ml are at greatest risk.[3]

Pantoprazole, a proton pump inhibitor, is used in peptic ulcers and other acid dyspeptic disorders of upper gastrointestinal tract in a dose of 40 mg orally once daily.[4] The effect of single oral dose of Pantoprazole 40 mg on preoperative gastric fluid *p*H and volume has not yet been studied.

Our aim of study was whether duodenogastric reflux[5] [transpyloric retrograde flow of alkaline duodenal contents in to the acidic gastric contents] significantly affect *p*H and volume of gastric contents and if yes, then whether a single oral dose of Pantoprazole 40 mg, administered a night before surgery, brings the *p*H ≥2.5 and volume ≤0.4 ml/Kg or ≤25 ml in adult patients undergoing elective surgery by excluding cases contaminated with duodenogastric reflux. Such samples do not represent true gastric contents rather alkaline duodenal fluid mixed with acidic gastric contents.

PATIENTS AND METHODS

The study protocol was approved by the University Hospital Research and Ethics Committee and written; informed consent was obtained from all the patients.

Patients and Group Assignment

We explored the effect of single oral dose of Pantoprazole 40 mg administered at 9:00 PM, a night before elective surgery, on intragastric *p*H and volume in adult 108 inpatients of American Society of Anaesthesiologists (ASA) physical status I–II, aged 15–70 years to be intubated with cuffed endotracheal tube.

Obese patients of Body Mass Index (BMI) more than 40 Kg/m^2, patients with upper gastrointestinal disorders, receiving medications known to affect the composition and volume of the stomach contents, Mallampati class IV and/or mouth opening less than 5 Cm and/or thyromental distance less than 6.5 Cm and/or history of documented difficult intubation, Diabetes Mellitus, intestinal obstruction and parturients were excluded from the study. Patients whose gastric aspirates contained bile salts due to duodenogastric reflux (DGR) or gastric contents were mixed with blood in the gastric tube were not included in the final statistical analysis while analysing *p*H and volume of

gastric contents because these samples are not true gastric contents rather alkaline duodenal fluid mixed with acidic gastric contents or blood mixed with gastric contents.

Patients were randomly assigned to one of the two groups by sealed enveloped method as follows (n=54 in each group): Group C (Placebo) and Group P (Pantoprazole). Age, sex, weight, height, BMI, ASA physical status, and the drug given were recorded for each patient. The medications were given orally with 20 ml of drinking water at 9:00 PM, a night before elective surgery. All patients also took oral diazepam 10 mg at the same time. All patients, according to the Hospital policy, remained nil per os (NPO) after 12 AM. Upon arrival in the waiting area of the operating room, patients were asked if they had been aware of any unusual feelings (side effects) like headache, gastrointestinal upset etc. after taking the medications, a night before elective surgery. This was also noted.

Collection and Analysis of Gastric Contents

After pre-oxygenation with 100% O_2 by face mask using four breaths vital capacity method, general anaesthesia was induced with injection fentanyl 1–2 µg/Kg, propofol 2–3 mg/Kg and rocuronium 0.6–0.9 mg/Kg. The lungs were ventilated taking care not to inflate the stomach. Maintaining cricoid pressure, trachea was intubated with cuffed endotracheal tube. All inductions were uneventful. After tracheal intubation, an endotracheal tube sized 8.0 mm internal diameter coated with paraffin liquid internally was passed orally in the oesophagus with anterior displacement of larynx. A predetermined length marked with adhesive tape (from Xiphoid process to ear lobules- and from ear lobules to nasal tip) of stomach tube[6] (Jamjoom Medical Industries, Jeddah, Saudi Arabia) sized 16 F was passed through this oesophageally placed endotracheal tube[7]. Placement of orogastric tube within the stomach was confirmed by auscultation over the epigastrium by injecting 10–15 ml of air. Gastric contents were gently aspirated manually with 60 ml of syringe by an investigator who was unaware of the group assignment. Applying and maintaining manual pressure over the epigastrium while the patient was in supine and then left and right lateral positions, orogastric tube was then manipulated to ensure maximum emptying of gastric contents. The orogastric tube was taken out followed by endotracheal tube placed in oesophagus. Any problem encountered during inserting or removing either the ore-oesophageally placed endotracheal tube or orogastric tube was also noted. The gastric contents were visually inspected for blood. The volume of gastric contents was measured with graduated syringe and *p*H with *p*H meter (Model 215 version 3.4, Denver Instrument Company, United States). The *p*H meter was calibrated using standard buffers at *p*H values of 4, 7 and 9.20. This *p*H meter has a precision of 0.01 units over the entire *p*H range. A minimum of 1 ml. volume of gastric contents was sufficient for *p*H determination with *p*H meter. Samples less than 1 ml. were considered as no gastric contents because a minimum volume of 1 ml. of gastric contents was sufficient for *p*H-metery. Using bile salts as a marker for bile, we applied qualitative Hay's Sulphur test to detect bile salts. A minimum volume of 1 ml. of gastric contents was sufficient to perform Hay's Sulphur test. In this test finely powered Sulphur is sprinkled upon the surface of cool (17 ºC or below) liquid. If bile salts are present Sulphur sinks down, sooner or later, in accordance with their percentage. If bile salts are present in from 1:5000 (0.02% or 200 µg/ml) to 1:10,000 (0.01% or 100 µg/ml) Sulphur at once begins to sink and all precipitated in 2 or 3 minutes; even in a dilution of 1:120,000 (0.0008% or 8.33 µg/ml) precipitation occurs. On the other hand if Sulphur remains floating on the surface, bile salts are absent.[8]

Time since premedication, time since *nil per os* (NPO), *p*H, volume of gastric contents and result of Hay's Sulphur test were also recorded for each patient. On the basis of Hay's Sulphur test, we further subdivided the Group C into Subgroups C-1 and C-2 and Group P into Subgroups P-1 and P-2 to observe the effect of duodenogastric refluxate on *p*H and volume of gastric aspirates.

Statistical Analysis

Statistical tests were performed using GraphPad Software, Inc., San Diego, United States, and results are expressed as absolute values (percentage) or Mean±SD.

Statistical comparisons between the two Groups C and P were carried out using two-tailed Student's (unpaired) t test for age, weight, height, BMI, time since premedication, time since NPO, *p*H and volume (Subgroups C-1, C-2, P-1 and P-2).

Fisher's exact test (two-tailed) was applied for sex, ASA physical status and risk of aspiration according to the criteria defined by Roberts and Shirley[9] (*p*H $\leq$2.5 and volume $\geq$0.4 ml/Kg or 25 ml). A p- value of less than 0.05 deemed statistically significant.

Power analysis revealed that the sample size (n= 30 in each group) of the study is sufficient to detect medium differences ([mean 1-mean 2]/SD= 0.5–0.7) in variables (*p*H and volume) at a significance level of 0.05 with the power of 0.6–0.8.[10]

RESULTS

One hundred and eight (108) adult inpatients undergoing elective General (n=54), Orthopaedic (n=25), Gynaecological (n=11), Urology (n=9), Thoracic (n=8) and Neuro (n=1) Surgery were studied. Physical characteristics of patients and timings of events are shown in Table-1. There was no statistically significant difference between the Groups C and P.

Table-1: Clinical characteristics of patients and timings of events.

Values are expressed as Mean±SD or numbers (percentage).

Physical characteristics of patients	Group C n=54	Group P n=54	*p*-Value
Age (years)	33.57 ±12.45	34.65 ±12.97	0.6616
Sex			
Male	27 (50%)	28 (51.85%)	1.000
Female	27 (50%)	26 (48.14%)	
ASA Physical Status			
Class-I	43 (79.62%)	38 (70.37%)	0.3743
Class-II	11 (20.38%)	16 (29.62%)	
Weight (Kg)	74.59 ±14.29	75.99 ±17.47	0.6482
Height (Cm)	162.10 ±7.79	163.25 ±10.14	0.5132
Body Mass Index (Kg/m^2)	28.52 ±5.57	28.44 ±5.43	0.9442
Timings of events			
Time since premedication (Min)	816.33 ±118.13	835.15 ±107.27	0.3882
Time since NPO (Min)	643.11 ±127.02	651.44 ±101.46	0.7072

We obtained gastric contents of 107 patients. One patient in Group P has no gastric contents while two samples (one from each Group) were mixed with blood. Hay's test was performed on 105 samples and was positive in 30 (28.57%) patients, 16 (6 males and 10 females) in Group C and 14 (7 males and 7 females) in Group P. The average (range) *p*H and volume of contaminated cases with duodenal contents were 5.75 (1.63–6.98) and 39.86 (5.0–96.0) ml and with blood were 7.13 (6.53–7.73) and 3.5 (3.0–4.0) ml. Samples contaminated with either duodenal fluid (30) or blood (2) were not considered as true gastric contents and not included in the final statistical analysis while analyzing *p*H and volume of gastric contents.

The *p*H and volume of all the Subgroups is shown in Table-2. Duodenogastric refluxate significantly affected both the *p*H and volume of gastric contents in both the Groups C (*p*-values 0.0009 and 0.0236, respectively) and Group P (*p*-value 0.0348 and 0.0003, respectively). The *p*H and volume of true gastric contents (Subgroups C-2 and P-2 is also shown in Table-2. Pantoprazole significantly affected both the *p*H (p=0.0118) and volume (p=0.0009) of gastric contents compared with placebo Group.

The proportion of the patients considered 'at risk' of significant lung injury should aspiration occur is shown in the Table-3 (after excluding contaminated samples with duodenogastric refluxate). There was a statistically significant difference between the Groups C-2 and P-2 (p 0.0324). No side effect of study drug was noted. All patients were discharged from the hospital without any problem.

Table-2: *p*H and volume of gastric contents (Mean±SD)

Variables	Group C n=54		Group P n=54	
	Group C-1 n=53	Group C-2 n=37	Group P-1 n=52	Group P-2 n=38
*p*H	2.85±1.90	1.75±0.47	3.73±2.09	2.85±1.69
Volume (ml)	25.79±18.61	18.09±9.68	19.32±14.34	12.68±8.43

Note: Samples contaminated either with blood (2) or no gastric contents (1) are not included in Subgroups C1 and P1. Group C-1 and Group P-1 include contaminated samples with duodenogastric refluxate as well. Group C-2 and Group P-2 represent true gastric contents. Comparison between the Subgroups *p*-value for pH (0.0009) and volume (0.0236) between Group C-1 and Group C-2. *p*-value for *p*H (0.0348) and volume (0.0003) between Group P-1 and Group P-2. *p*-value for *p*H (0.0118) and volume (0.0009) between Group C-2 and Group P-2.

Table-3: Patients at risk according to defined criteria (n (%))

Variables	Group C-2 n=37	Group P-2 n=38	*p*-value
Patients with *p*H ≤2.5	35 (94.59%)	23 (60.52%)	0.0006
Patients with volume ≥25 ml.	13 (35.13%)	8 (21.05%)	0.2018
Patients with *p*H ≤2.5 and volume ≥25 ml.	13 (35.13%)	5 (13.15%)	0.0324

Note: Samples mixed either with duodenal contents (30) or blood (2) or having no contents (1) are not included in Subgroups C-2 and P-2.

DISCUSSION

Many pharmacological attempts, including the use of H_2-receptor antagonists, proton pump inhibitors (PPIs) and antacids have been made to reduce the risk of pulmonary aspiration by decreasing acidity and volume of gastric fluid.[9] Pantoprazole, developed in Germany in 2000, is the third proton pump inhibitors after omeprazole and Lansoprazole[11] used in clinical practice. 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.

There is only one study available that was conducted to evaluate the effect of intravenous Pantoprazole and ranitidine for improving preoperative gastric fluid properties in adults undergoing elective surgery.[12] In this study all drugs were given intravenously one hour before surgery. In our study the Mean±SD, *p*H, volume and proportion of patients at risk are 2.85±1.69, 12.68±8.43 ml and 13.15% compared with intravenous Pantoprazole 5.30±1.84 (p<0.0001), 15.20±15.52 ml (p=0.7166) and 10% (p=1.0000), respectively. The primary out come of the study, the proportion of patients at risk is almost the same. A better aspect in our study may be the exclusion of all

duodenogastric refluxate contaminated samples. In this current study 30 samples out of 105 were positive for bile salts in their gastric aspirates. This is, no doubt, a big number and if unfortunately, patient aspirates it will damage the lungs as well. We should have included a prokinetic agent to get rid of duodenogastric refluxate. More work is requires in this regard.

Mendelson CL described the aspiration of gastric contents (Mendelson's syndrome) in 1946 in obstetrical cases.[13] Since then extensive work has been done and reported in anaesthesia literature. In all the previous studies conducted, importance of duodenogastric reflux (DGR), as a possible factor that can affect both the *p*H and volume of gastric contents, has never been addressed. Duodenal contents consist of bile, pancreatic juice, small intestine and Brunner's gland secretion. All these secretions are alkaline in nature due to HCO_3^- ions.[14] When duodenal contents flow in retrograde fashion, then mix with acid and Pepsin[5] in the stomach and bring the *p*H towards less acidity thus affecting *p*H and at the same time increase the volume of gastric contents similar to oral ingestion of sodium citrate. To overcome this problem, first, we aspirated gastric contents in optimal position of the patient as described by Niinai *et al.*[15] Secondly, we passed a predetermined length of stomach tube so that it should not go beyond pyloric sphincter. Thirdly, we excluded those samples that were positive for Hay's Sulphur test while analysing final *p*H and volume of gastric contents.

In this current study, we passed gastric tube through an endotracheal tube passed blindly in the oesophagus. Although, this technique of passing stomach tube is old[7], but no body has utilised it for sampling gastric contents in any previous study. Importantly this technique can avoid contamination of gastric contents with pooled saliva in pharynx during inserting, manipulating or removing gastric contents.[16] Insertion of oropharyngeal airway, act of laryngoscopy and tracheal tube insertion are the stimulants that increase the production rate of saliva and saliva pools due to the lack of swallowing reflex in pharynx.

In this study two samples were found to be mixed with blood due to gastric mucosal entrapment. Gastric mucosal entrapment occurs particularly when air and fluid has been aspirated and stomach is collapsed. Gastric mucosa is caught into the side holes of stomach even with gentle suction effect. Bleeding may occur and can be seen in stomach tube thus giving *p*H of blood mixed with gastric contents rather than pure gastric contents. It is commonly believed that the sump tubes (double-lumen) are more effective than the single lumen variety, but there is no scientific evidence to support this view.[17] However, any sample containing any amount of visible blood mixed with gastric contents was not considered true sample and was not included in the analysis for *p*H, volume and Hay's Sulphur test.

We applied Hay's Sulphur test to detect bile salts in the gastric contents. This simple, sensitive and fairly reliable test depends on the principal that bile salts have the property of reducing the surface tension of fluids in which they are contained[18], was devised in1886 by Matthew Hay (1855–1932).

In this present study, total gastric volume may have been underestimated by the blind aspiration via gastric tube in each patient due to the functional divisions of the stomach into antral and fundal sacs.[19] A similar error would occur in all patients of both groups and inter-group comparisons are, therefore, valid. Due to difficulty in accurate measurement of gastric fluid volume, *p*H is a better marker for aspiration assessment.

CONCLUSION

Oral Pantoprazole 40 mg administered a night before elective surgery does improve the gastric environment, excluding those samples contaminated with duodenogastric reflux, and at the time of induction of anaesthesia may prove to be useful in decreasing risk of aspiration due to gastric contents.

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