

PRE-ANAESTHETIC ORAL LANSOPRAZOLE FOR THE PROPHYLAXIS OF MENDELSON'S SYNDROME AND IMPACT OF DUODENOGASTRIC REFLUX ON pH AND VOLUME OF GASTRIC CONTENTS

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Background. Lansoprazole, a proton pump inhibitor, is used in peptic ulcers and other acid dyspeptic disorders. The aim of this study is to determine whether a single oral dose of lansoprazole 30 mg, administered a night before surgery, is effective on pH and volume of gastric contents after excluding those samples contaminated with duodenogastric refluxate (DGR).

Patients and Methods. This clinical trial was conducted in 112 adult patients of both sex, ASA physical status I-II, and aged 15-70 yr. The patients in group C (control) received placebo while group L (lansoprazole 30 mg) orally at 9.00 p.m., 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 esophagus after tracheal intubation and analyzed for the presence of bile salts, pH and volume.

Results. Thirty three samples (30 %) out of 110 were contaminated with duodenal contents. DGR significantly affected the pH and volume in both the groups. Lansoprazole, after excluding those samples contaminated either with duodenal fluid or blood, significantly increased pH ($P < 0.0001$), decreased volume ($P = 0.0326$) and the proportion of the patients (10.52 % versus 30.76%) considered "at risk" compared with Placebo ($P = 0.0475$) according to the criteria defined ($pH \leq 2.5$ and volume ≥ 25 ml).

Conclusions. Lansoprazole 30 mg given orally at 9.00 p.m., a night before surgery, significantly decreased the number of patients at risk of aspiration pneumonia at the time of induction of anesthesia if the aspiration of gastric contents occurs.

Keywords. Aspiration; Duodenogastric refluxate; Gastric pH and volume; Lansoprazole.

Introduction

PULMONARY ASPIRATION OF GASTRIC contents is the inhalation of gastric contents into the larynx and lower respiratory tract. Its severity depends upon the nature (pH) and amount (volume) of the aspirated material and the host's factors that predispose the patient to aspirate.¹ General anesthesia itself is a major risk factor that predisposes the patient to aspirate due to the loss of protective airway reflexes. The principle of protecting the airways prophylactically by pharmacological method forms one of the cornerstones of the practice of anesthesiology. Lansoprazole, a proton pump inhibitor, is used in peptic ulcers and other acid dyspeptic disorders of upper gastrointestinal tract in a dose of 30 mg orally once daily.² The aim of the

study was to determine whether a single oral dose of lansoprazole 30 mg, administered a night before surgery, is effective in increasing the $pH \geq 2.5$ and decreasing volume ≤ 0.4 ml/kg or 25 ml at the time of induction of anesthesia, in adult patients undergoing elective surgery by excluding those cases contaminated with DGR. To the best of our knowledge, the impact of DGR on gastric pH and volume has never been addressed in any previous study.

Patients and Methods

The study was approved by the College of Medicine Research Center (CMRC) and College Ethics Committee. Written informed consent was obtained from all patients. We examined the effect of single oral dose of lansoprazole 30mg, administered at 9.00 p.m., a night before elective surgery, on intragastric pH and volume in adult 112

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inpatients of either sex, aged 15-70 yr of ASA physical status I-II, to be intubated with cuffed endotracheal tube from August 2006 to October 2006. Patients with upper gastrointestinal disorders, body mass index (BMI) > 40 kg/m², receiving medications known to affect the secretory and /or motor functions of the stomach, Mallampati class IV and/or mouth opening less than 5 cm and /or thyromental distance less than 6.5 cm and/or history of difficult intubation, intestinal obstruction, parturients and diabetes mellitus were excluded from the study. Patients who were premedicated and their gastric aspirates contained duodenal fluid due to DGR or gastric contents were mixed with blood in the gastric tube were not included in the final statistical analysis while analyzing pH 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. We repacked the placebo and lansoprazole tablets in 112 envelopes of the same size, shape and color and their names were changed as either drug one or drug five by a person who was not taking part in the study to keep the patients and investigators blinded of it. The group assignment paper was sealed in another envelope that was opened to know which drug corresponds to either drug one or drug five after the statistical analysis. On the pre-operative anesthesia visit, a day before surgery, the nature and purpose of the study was explained to each patient. We asked each patient to pick up only one envelope from the envelopes (randomization). Thus, the patients were allocated either to group C (control) or group L (lansoprazole) randomly by sealed envelope method. Age, sex, weight, height, BMI, ASA physical status, and the drug given were recorded for each patient. These drugs were given orally with 20 ml of drinking water at 9.00 p.m., a night before elective surgery. The patients also received oral diazepam 10 mg at the same time. According to the hospital policy, all patients were fasted from 12 midnight. Upon arrival in the waiting area of the operating room, all patients were asked if they had been aware of any untoward effects after taking the study drug, a night before surgery. It was also recorded. In the operating room, routine monitors were attached to the patients and turned on. After pre-oxygenation with 100 % O₂ by face mask using four breaths vital capacity method, anesthesia 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. Placement and position of endotracheal tube was confirmed with EtCO₂ monitor and then secured properly. After establishing stable anesthesia, an endotracheal tube sized 8.5 mm coated with paraffin liquid internally as well as externally was passed via oral route in the esophagus with anterior displacement of larynx. A predetermined length marked with adhesive tape (Xiphoid process to ear lobules- from ear lobules to nasal tip) of stomach tube³ (Jamjoom Medical Industries, Jeddah, Saudi Arabia) sized 18 F was passed through this esophageally placed endotracheal tube.⁴ Placement of this tube within the stomach was verified by auscultation over the epigastrium during insufflation of 10-15 ml of air. Gastric contents were gently aspirated manually with 60 ml of syringe by an investigator who was blinded of the group assignment. Applying manual pressure over the epigastrium while the patient was in supine and then left and right lateral positions, gastric tube was then manipulated to ensure maximum emptying of gastric contents. The stomach tube was removed followed by esophageally placed endotracheal tube. Any problem encountered during inserting or removing the oro-esophageally placed endotracheal tube or gastric tube was also recorded. The volume of gastric contents was measured with graduated syringe and pH with pH meter (Model 215 version 3.4, Denver Instrument Company, US). The pH meter was calibrated using standard buffers at pH values of 4, 7 and 9.20. This pH meter has a precision of 0.01 units over the entire pH range. A minimum of 1 ml volume of gastric contents was sufficient for pH determination with pH meter. In case of very little amount of gastric contents, we cut the stomach tube and aspirated gastric material with disposable plastic pipette. Samples less than 1 ml were considered as no gastric contents because a minimum volume of 1 ml of gastric contents was sufficient for pH- metery. Using bile salts as a marker for bile, we applied qualitative Hay's sulphur test for the presence of bile salts. A minimum volume of 1 ml of gastric contents was adequate to perform Hay's sulphur test. In this test finely powdered sulphur is sprinkled upon the surface of cool (17 °C 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 200µg/ml) to 1:10,000(0.01 % or 100µg/ml) sulphur at once begins to sink and all precipitated in 2 or 3 min; even in a dilution of 1:120,000 (0.0008 % or 8.33 µg/ml) precipitation occurs.⁵ On the other hand, if sulphur remains floating on the surface, bile salts are absent. Anesthesia was maintained with air, O₂ and sevoflurane. The patients also received incremental doses of fentanyl and rocuronium as required. At the end of surgery, injection of atropine and neostigmine were given to antagonize the residual effect of rocuronium. The trachea was extubated in lateral position and patients were transferred to the recovery room.

Time since premedication, time since NPO, pH, 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 divided the group C into group C-1(contaminated with DGR) and group C-2 (non-contaminated with DGR) and group L into group L-1(contaminated with DGR) and Group L-2 (non-contaminated with DGR) to see the impact of DGR on pH and volume of gastric contents.

Statistical tests were performed using GraphPad Software, Inc., San Diego, United States, and results are expressed as absolute values (percentage) or mean \pm standard deviation (SD). Statistical comparisons between the two groups 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 (pH \leq 2.5 and volume \geq 0.4 ml/kg or 25 ml). A p- value of less than 0.05 was considered statistically significant. Power analysis revealed that the sample size (n=30 in each group) of the study was sufficient to detect a difference of 0.7 between groups in gastric pH and volume at a significance level of 0.05 (= α) with a power of 0.85.⁶

Results

One hundred and twelve adult patients undergoing elective general (n=60), orthopedic (n=25), gynecological (n=14), urology (n=5), and thoracic (n=4), neuro (n = 3) and maxillofacial (n =1) surgery were studied. Physical characteristics of patients and timings of events are shown in Table 1.

Table 1. Physical characteristics of patients and timings of events (mean \pm SD or %)

	Group C	Group L	P-value
Age (yr)	35.2 \pm 13.5	37.4 \pm 12.8	0.3850
Sex			1.0000
Male	28 (50%)	28 (50%)	
Female	28 (50%)	28 (50%)	
ASA			1.0000
Class – I	41 (73.21%)	42 (75%)	
Class – II	15(26.78 %)	4 (25%)	
Weight (Kg)	75.0 \pm 13.5	70.3 \pm 15.5	0.1029
Height (cm)	161.2 \pm 7.8	160.2 \pm 7.8	0.7507
BMI (kilograms/ meter ²)	28.9 \pm 5.5	27.7 \pm 4.2	0.2002
Time since premedication (min)	829.5 \pm 137.2	824.6 \pm 130.1	0.8463
Time since NPO (min)	659.8 \pm 139.0	648.0 \pm 130.8	0.6444

Table 2. Characters of gastric aspirate.

	Group C	Group L	Total
Sample with no gastric contents	0	1	1
Samples mixed with blood	1	0	1
Samples available for Hay's sulphur test	55	55	110
Samples mixed with duodenal contents	16	17	33

There was no statistically significant difference between the two groups regarding age, sex, ASA physical status, weight, height, BMI, time since premedication and time since NPO.

We obtained gastric contents of 111 patients. One patient had no gastric contents. Hay's test was performed on 110 samples and was positive in 33 patients (30 %) while one sample was mixed with blood; the details are shown in Table 2. The average (range) pH and volume of contaminated cases with duodenal contents 5.90 ml (1.63 -6.98 ml) and 71.81 ml (9.0-118.0 ml) and with blood was 7.13 (4.0) ml. These cases were considered as contaminated and not included in statistical analysis while analyzing pH, volume of gastric contents. DGR significantly affected both the pH and volume of gastric contents in both Groups C and L as shown in Table 3. The proportion of the patients considered "at risk" of significant lung injury should aspiration occur is shown in Table 4 after excluding contaminated samples with DGR. There was a statistically

significant difference between the two groups C-2 and L-2 when pH and volume both were combined ($P=0.0475$). All patients were discharged from the hospital without any problem.

Table 3. pH and volume of gastric contents (mean±SD)

Variables	Group C		Group L	
	Group C-1	Group C-2	Group L-1	Group L-2
Number of patients (n)	n = 55	n = 39	n = 55	n = 38
pH	2.9±1.8	1.9±0.4	4.2±2.1	3.2±1.9
Volume (ml)	35.3±31.6	19.6±18.5	29.7±32.0	11.8±11.9

Table 4. Patients at risk (values are expressed as numbers or %)

Variables	Group C-2 n = 39	Group L-2 n = 38	P- value
Patients with pH ≤ 2.5	37(94.87 %)	18(47.36 %)	<0.0001
Patients with volume ≥ 25 ml	12(30.76 %)	4(10.52%)	0.0475
Patients with pH ≤ 2.5 and volume ≥ 25 ml	12(30.76%)	4(10.52%)	0.0475

Discussion

Regurgitation, vomiting and aspiration may occur quite unexpectedly in association with anesthesia and may have serious sequelae. Aspiration/regurgitation was ranked fifth and comprised over 5% of a large collection of incidents that arose during general anesthesia⁷. While attention has usually focused on aspiration as the major consequences of regurgitation and vomiting, other sequelae such as laryngospasm, desaturation and bronchospasm are also important. These problems are encountered by all practicing anesthetists and present as emergencies requiring instant recognition and a rapid appropriate response. Many pharmacological attempts, including the use of H₂ – receptor antagonists, proton pump inhibitors (PPIs) and antacids have been made to eliminate the risk of pulmonary aspiration by decreasing acidity and volume of gastric fluid.⁸ Hett et al⁹ studied lansoprazole 30 and 60 mg given orally at 22.00 hours in patients undergoing elective surgery. The mean (range) pH and volume in group lansoprazole 30 mg were 2.46(1.47-4.36) and 27.3 ml (0-55 ml). Patients with gastric pH < 2.5 and volume > 25 ml were 33 % and 41% respectively. Nishina et al⁸ compared the efficacy of lansoprazole, omeprazole and ranitidine in different dosages for reducing

preoperative gastric secretion in adult patients undergoing elective surgery. Lansoprazole- placebo group received 30 mg at 21.00 hours. The mean (SD) pH and volume in this group were 2.7±1.3 and 0.31±0.28 ml/kg respectively. Patients at risk as defined by the criteria of pH < 2.5 and volume of 0.4 ml/kg were 24%. When compared to our results, pH and volume are comparable but proportions of patients at risk are far more than to our reported values. Aspiration of gastric contents (Mendelson's syndrome) was first described by Mendelson CL in 1946 in obstetrical cases.¹⁰ In all the previous studies conducted, importance of DGR, as a possible factor that can affect both the pH and volume of gastric contents, has not been addressed. DGR, the transpyloric retrograde flow of duodenal contents into the stomach, is well established clinical entity^{11, 12, 13, 14, 15} with variable incidence. Mild to moderate DGR occurs in approximately one third (33%) of normal subjects, and in one third (33%) of patients with non-ulcer dyspepsia as shown by the radiological tests of Keet¹⁶ and Huges et al,¹⁷ in other words, the pylorus is normally not competent in a significant percentage of normal subjects and approximately the same percentage of patients with non-ulcer dyspepsia. Wolverson et al¹⁸ studied the incidence of DGR in peptic ulcer disease using 99mTc Hydroxy Iminodiacetic acid (HIDA) scan, with a gamma camera in the supine position in control patients and patients with active duodenal ulceration. Cholecystokinin was injected intravenously during the test to contract the gall bladder. Sixty patients with benign gastric ulcers were investigated for DGR in the sitting position by a nasogastric aspiration technique after 10 % dextrose meal, 32 patients (53%) were with positive reflux. The incidence of DGR assessed supine in the fasting state, and seated after a liquid meal, was similar in patients with peptic ulceration and in normal controls. In healthy subjects, DGR occurs sporadically in the interdigestive states. Its underlying mechanisms are poorly understood.¹⁹ Our reported incidence 29.66 % is comparable to previously reported studies. Duodenal contents consist of bile (volume 1000 ml /day: pH 7.8), pancreatic juice (volume 1000 ml/day: pH 9.0-8.3), small intestine secretion (volume 1800 ml/day: pH 7.5-8.0) and Brunner's gland (volume 200 ml/day: pH 8.0-8.9). All these secretions are, of course, alkaline in nature due to HCO₃⁻ ions.²⁰ When duodenal contents flow in retrograde fashion, then

mix with acid and pepsin¹⁴ in the stomach and bring the pH towards less acidity thus affecting pH and at the same time increase the volume of gastric contents similar to oral ingestion of sodium citrate. To overcome this problem, firstly, we aspirated gastric contents in optimal position of the patient as described by Niinai et al.²¹ 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 analyzing pH and volume of gastric contents. Lastly, the average volume of contaminated cases with duodenal contents was 71.81 ml (9.0-118.0 ml) that can only be aspirated from storage organ like stomach. In the current study, we passed gastric tube through an endotracheal tube passed blindly in the esophagus. Although, this technique of passing stomach tube is old, has not been utilized for sampling gastric contents in any previous study. We obtained number of advantages with this technique. Firstly, under general anesthesia swallowing reflex is depressed and in an intubated patient, the esophagus may be occluded by inflated endotracheal tube cuff and can interfere with stomach tube insertion. Secondly, this technique also avoids finding the upper esophageal opening and coiling of the tube in the mouth even after successfully passing the distal end of tube into stomach. Thirdly, manipulation of gastric tube in and out during different positions was very easy giving minimal trauma to patients. Lastly, we avoided theoretical possibility of contamination of gastric contents with pooled saliva in pharynx during inserting, manipulating or removing gastric contents. In the awaked state, the basal rate of saliva production is about 0.5 ml/min, but this may increase to 5 ml/min with intense stimulation.²² Firstly, insertion of oropharyngeal airway, act of laryngoscopy and tracheal tube insertion are the stimulants that increase the production rate of saliva. Secondly, saliva pools due to the lack of swallowing reflex in pharynx. Thirdly, in an intubated patient, the esophagus may be occluded by inflated endotracheal tube cuff. It is difficult to pass stomach tube without the entry of saliva through the side holes into the tube because the stomach tubes do not have obturator as we use in tracheotomy tubes. 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 tube even with gentle suction effect. Bleeding may occur and can be seen in stomach tube thus giving pH 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.²³ However, any sample containing any amount of visible blood mixed with gastric contents was not considered for pH and volume analysis. The BilitecTM 2000 ambulatory bile reflux recorder is currently the only commercially available device that is proven effective in measuring bile reflux.²⁴ Using bilirubin as a marker for bile, the Bilitec 2000 recorder captures the frequency and duration of bile exposure either in the stomach or esophagus over a 24 hr period. This method was not feasible for us we applied Hay's sulphur test to detect bile salts in the gastric contents. This simple, sensitive and fairly reliable test²⁵ depends on the principal that bile salts have the property of reducing the surface tension of fluids in which they are contained,²⁶ was devised in 1886 by Matthew Hay (1855-1932). The common techniques to aspirate the residual volume of gastric contents are fiberoptic gastroscopy, indicator dilution technique and blind aspiration via gastric tube. In the current 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.²⁷ This method is simple, inexpensive, and easy to perform and has been widely used in the similar studies.

In conclusion, DGR significantly affected both the pH and volume of gastric contents. Oral lansoprazole 30 mg administered a night before elective surgery (after excluding contaminated cases with DGR) did improve the gastric environment at the time of induction of anesthesia, if aspiration of gastric contents occurs.

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