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Effect Of Single Oral Dose Of Omeprazole Administered
Before Surgery On The Intragastric PH And Volume In A
Patients Undergoing Elective Surgery With And Without
Duodenogastric Reflux

A Triple Blind Placebo Controlled Clinical Trial.

SUMMARY

Aspiration of gastric contents is rare, but serious and life threatening complicat
general anaesthesia. Its severity depends upon the pH and volume of gastric c
This prospective, triple blind, randomized and placebo controlled clinical trial w
conducted to evaluate the effect of preanaesthetic administration of oral Omep
pH and volume of gastric contents in 112 adult inpatients of either sex, Americ
of Anesthesiologists(ASA) physical status I-II, and aged 15-70 years. The pati
Group C (Control) received Placebo while Group O (Omeprazole 40 mg) orally
p.m., a night before elective surgery. Next day, Gastric contents were aspirate
large bore, multi-orifices gastric tube passed through an endotracheal tube pla
in esophagus after tracheal intubation and analyzed for the presence of bile sal
volume. Thirty one samples (27.92 %) out of 111 were contaminated with duo
contents. One patient has no gastric contents. Duodenogastric reflux significan
pH and volume of gastric contents in both groups (C1 versus C2: p value for p
(0.0012) & volume (0.0082) and O1 versus O2: p value for pH (0.0341) & vol
(0.0016). Omeprazole, after excluding contaminated cases with duodenogastri
decreased significantly the pH (p <0.0001), volume of gastric contents (p 0.02
proportion of the patients (4.87% versus 30.76%) considered" at risk" compar
Placebo (p 0.0028) according to the criteria defined (pH ≤ 2.5 and volume ≥ 25
Duodenogastric reflux significantly affected the pH and volume of gastric conte
Omeprazole 40 mg given orally at 9.00 p.m. provided adequate prophylaxis for
aspiration syndrome, excluding all the cases contaminated with duodenogastri

KEY WORDS: Aspiration, duodenogastric refluxate, gastric pH& volume, Omeprazole.

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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 potential 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.

Omeprazole, a proton pump inhibitor, is used in peptic ulcers and other acid dyspeptic disorders of upper gastrointestinal tract in a dose of 20-40 mg orally once daily 2.

Our aim of study was to determine whether (a) duodenogastric reflux significantly affect the pH and volume of gastric contents. (b) a single oral dose of Omeprazole 40 mg, administered a night before surgery, is effective in increasing the pH ≥ 2.5 and ≤ 0.4 ml/kg or 25 ml in adult patients undergoing elective surgery by excluding those cases contaminated with duodenogastric refluxate. While evaluating the usefulness of omeprazole as prophylaxis for acid aspiration syndrome, the impact of duodenogastric refluxate on gastric pH and volume has never been reported 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 the patients.

PATIENTS AND GROUP ASSIGNMENT

We examined the effect of single oral dose of Omeprazole 40mg, administered at 9.00 p.m., a night before elective surgery, on intragastric pH and volume in adult 112 inpatients of either sex, aged 15-70 years of American Society of Anesthesiologists (ASA) physical status I-II, to be intubated with cuffed endotracheal tube.

Patients with upper gastrointestinal disorders, Body Mass Index (BMI) more than 40 kg/m2, receiving medications known to affect the secretory and /or motor functions of the stomach, Mallampati class V and /or mouth opening less than 5 centimeters and /or thyromental distance less than 6.5 centimeters and/or history of difficult intubation, intestinal obstruction, parturients, Diabetes Mellitus were excluded from the study. Patients who were premedicated and their gastric aspirates were contained duodenal fluid due to duodenogastric reflux (DGR) were not included in the statistical analysis while analyzing final pH and volume of gastric contents because these samples were not true gastric contents rather alkaline duodenal fluid mixed with acidic gastric contents.

We repacked the Placebo and Omeprazole capsules in 112 envelopes of the same size, shape and color and their names were changed as either Drug One or Drug Six 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 Six 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 O (Omeprazole) 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., the 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 unusual feelings (side effects) after taking the study drug, a night before surgery.

COLLECTION AND ANALYSIS OF GASTRIC CONTENTS

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 internal diameter 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 tube 3 (Jamjoom Medical Industries, Jeddah, Saudi Arabia) sized 18 F was passed through this esophageally placed endotracheal tube4. 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 contents5. 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, United States). 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 one-milliliter 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 one- milliliter were considered as no gastric contents because a minimum volume of one- milliliter of gastric contents was sufficient 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 one milliliter of gastric contents was adequate to perform Hay's Sulphur test. In this test finely powered Sulphur is sprinkled upon the surface of cool (17 0C 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 two or three minutes; even in a dilution of 1:120,000 (0.0008 % or 8.33 µg/ml) precipitation occurs6.

On the other hand, if Sulphur remains floating on the surface, bile salts are absent. Anaesthesia was maintained with Air, O2 and sevoflorane. The patients also received incremental doses of fentanyl and rocuronium as required. At the end of surgery, injection atropine and neostigmine were given to antagonize the residual effect of rocuronium. All patients were extubated in lateral position and then transferred to recovery room.

Time since premedication, time since *Nil Per Os.* (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(including contaminated samples with duodenogastric refluxate) and Group C-2 (non-contaminated with duodenogastric refluxate) and Group O into Group O-1(including contaminated samples with duodenogastric refluxate) and Group O-2 (non-contaminated with duodenogastric refluxate) to see the impact of duodenogastric refluxate on pH and volume of gastric contents in both the groups.

STATISTICAL ANALYSIS

Statistical tests were performed using GraphPad Software, Inc., San Diego, United States, and results are expressed as absolute values (percentage) or mean ± 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 ≤ 2.5 and volume ≥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 7.

RESULTS

One hundred and twelve (112) adult inpatients undergoing elective General (n=60), Orthopedic (n=21), Gynecological (n=18), Urology (n=7), and Thoracic (n=4), and Neuro (n = 2) Surgery were studied. Physical characteristics of patients and timings of events are shown in Table 1. 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 has no gastric contents. Hay's test was performed on 111 samples and was positive in 31 patients (27.92 %). The detail is shown in Table 2.

Table 1: Physical characteristics of patients and timings of events. Values are expressed either as mean±SD or numbers (percentage).

Physical characteristics of patients	Group C n = 56	Group O n = 56	p-value
Age (years)	35.29± 13.58	39.18±13.31	0.1284
Sex Male Female	28 (50%) 28 (50%)	28 (50%) 28 (50%)	1.0000
ASA physical status Class – I Class – II	42 (75%) 14 (25 %)	40 (71.42%) 16 (28.57%)	1.0000
Weight (kilograms)	75.04± 14.60	76.36± 13.40	0.6202
Height (centimeters)	161.25± 7.83	161.37±11.57	0.5936
Body Mass Index (kilograms/ meter2)	28.96± 5.54	29.51± 5.33	0.5936
Timings of events			
Time since premedication (minutes)	759.34 ±83.56	745.14±69.62	0.3308
Time since NPO (minutes)	585.88±83.69	566.93±66.00	0.1862

Table 2. Facts and figures about gastric aspirate.

Groups	Group C	Group O	Total
No. of cases	56	56	112
Male	28	28	56
Female	28	28	56
Patients with no gastric contents	1	0	1
Samples available for Hay's Sulphur test	55	56	111
Samples mixed with duodenal contents	16	15	31
Male	7	6	13
Female	9	9	18

The average (range) pH and volume of contaminated cases with duodenal contents 5.84 (1.63 -6.98) and 77.93 (9.0-95.0) ml. These cases were considered as contaminated and not included in statistical analysis while analyzing pH, volume of gastric contents.

Duodenogastric refluxate significantly affected both the pH and volume of gastric contents in both Groups as shown in Table 3. There was a statistically significant difference between the two Groups C-2 and O-2 (non- contaminated samples with duodenogastric refluxate) regarding pH ($p < 0.0001$) and volume (p 0.0238) of gastric contents.

Table 3. pH and volume of gastric contents. Values are expressed as mean± SD.

Groups	Group C n = 56		Group O n = 56	
Subgroups	Group C -1 n = 55	Group C-2 n = 39	Group O-1 n = 56	Group O-2 n = 41
pH	2.91±1.85	1.90±0.47	4.14 ±1.87	3.37±1.54
Volume(milliliters)	35.70±31.33	20.62±17.99	31.44±35.21	12.87±11.52

Note:

Group C-1 and GroupO-1 include contaminated samples with duodenogastric refluxate.

Group C-2 and Group O-2 include non-contaminated samples.

Comparisons between the groups

pH and volume between Group C-1 and Group C-2 (p value 0.0012 and 0.0082).

pH and volume between Group O-1 and Group O-2 (p value 0.0341and 0.0016).

pH and volume between Group C-2 and Group O-2 (p value <0.0001 and 0.0238).

The proportion of the patients considered" at risk" of significant lung injury should aspiration occur is shown in the Table 4 after excluding contaminated samples with duodenogastric refluxate. There was a statistically significant difference between the two Groups (p 0.0028).

Table 4. Patients at risk according to defined criteria. Values are expressed as numbers (percentage).

Variables	Group C-2 n =39	Group O-2 n = 41	p-value
Patients with pH ≤ 2.5	37 (94.87%)	16(39.02%)	<0.0001
Patients with volume ≥25 ml	12 (30.76%)	5 (12.19%)	0.0567
Patients with pH ≤ 2.5 and volume ≥25 ml	12 (30.76%)	2 (4.87%)	0.0028

Note.
Samples mixed either with duodenal contents (31) or having no contents (1) are not included.

One patient in Group C had severe bronchospasm at induction. No side effect was reported. All patients were discharged from the hospital without any problem.

DISCUSSION

Regurgitation, vomiting and aspiration may occur quite unexpectedly in association with Anaesthesia and may have serious sequelae. Aspiration/regurgitation was ranked fifth and comprised over 5% of a large collection of incidents that arose during general Anaesthesia8. While attention has usually focused on aspiration as the major consequences of regurgitation and vomiting, other sequale such as laryngospasm, desaturation and bronchospasm are also important. These problems are encountered by all practicing anaesthetists 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 9. We searched on PubMed under "aspiration of gastric contents and omeprazole" and found 11 studies. These studies did not match exactly with our study. However, we compared our results with those studies which were very close to our study. Prieto et al 10 studied the efficacy of different doses of omeprazole for the prophylaxis of acid aspiration syndrome. The pH (mean ± SD) of gastric contents was 4.87±2.35 of that group in whom patients received oral Omeprazole 40 mg the night prior to surgery. The incidence of pH less than 1.5 was 4% and the concluded that premedication with 40 mg of oral omeprazole the night prior to surgery increases pH up to safe values for the prophylaxis of the acid aspiration syndrome. Gouda et al11 compared the effects of ranitidine and omeprazole on volume and pH of gastric contents in elective surgical patients and found that 14.2 % patients of group treated with omeprazole 40 mg orally the evening before surgery were at risk according the criteria defined (pH <2.5 and volume

>25 ml. Wingtin et al12 found pH was less than 3.5 only in 4.5% of those who received omeprazole 40 orally a night before surgery. Mean (SEM) volume of gastric fluid was 9.2 (1.8) ml in this group. They concluded that a single oral dose of 40 mg omeprazole significantly decreased the number of patients at risk of aspiration pneumonitis. Vila et al 13 compared the effects of single oral doses of omeprazole 40 mg, famotidine 40 mg or placebo on gastric secretion in 45 non-obese patients the night before elective biliary surgery. They found that Famotidine, but not omeprazole, produced a significant decrease in gastric volume and acidity. Patients were considered to be at risk if pH < 2.5 and volume > 0.4 ml.kg-1. Three patients in the omeprazole group came into this category. They concluded that a single oral dose of omeprazole 40 mg given the night before surgery does not afford adequate prophylaxis for acid aspiration syndrome. When compared to these results, our results are more accurate because we excluded all the contaminated samples with duodenogastric refluxate.

Aspiration of gastric contents (Mendelson's syndrome) was first described by Mendelson CL in 1946 in obstetrical cases 14. Since then a lot of work has been done and published in the form of brief reports, forums, original papers, editorials and review articles in anesthesia literature. In all the previous studies conducted, importance of duodenogastric reflux (DGR), as a possible factor that can affect both the pH and volume of gastric contents, has never been addressed. Duodenogastric reflux, the trans-pyloric retrograde flow of duodenal contents into the stomach, is well known, well established clinical entity 15, 16, 17, 18, 19 with variable incidence. Mild to moderate duodenogastric reflux 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 Keet 20 and Huges et al 21, 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 22studied the incidence of duodenogastric reflux 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. Patients with benign gastric ulcers, and a group of age matched controls, were investigated for duodenogastric bile reflux in the sitting position by a nasogastric aspiration technique after 10 % dextrose meal. Of 60 patients with duodenal ulceration 32(53%) were reflux positive, and of 13 control patients 6 (46%) were positive. Of 30 patients with gastric ulceration 17 (53%) were reflux positive, and of 8 out of 15 (53%) control subjects were positive. The incidence of duodenogastric reflux 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, duodenogastric reflux occurs sporadically in the interdigestive states. Its underlying mechanisms are poorly understood 23. Our reported incidence 29.66 % is comparable to previously reported above mentioned 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 HCO_3^- ions 24. When duodenal contents flow in retrograde fashion, then mix with acid and Pepsin18 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 5. 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 (range) volume of contaminated cases with duodenal contents was 77.93 (9.0-95.0) ml that can only be aspirated from storage organ like stomach.
In this current study, we passed gastric tube through an endotracheal tube passed blindly in the esophagus. Although, this technique of passing stomach tube is old 4, but no body has utilized it for sampling gastric contents in any previous study. We obtained number of advantages with this technique. Firstly, under general anaesthesia 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/minute, but this may increase to 5ml /minute with intense stimulation 25. 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.

The BilitecTM 2000 ambulatory bile reflux recorder is currently the only commercially available device that is proven effective in measuring bile reflux 26. 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-hour 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 test 27 depends on the principal that bile salts have the property of reducing the surface tension of fluids in which they are contained 28, was devised in1886 by Matthew Hay (1855-1932).

One of our patients had severe bronchospasm at intubation. Fiberoptic bronchoscopy did not support the evidence of aspiration of gastric contents. This patient was scheduled for thoracoscopic sympethectomy. A chest tube was inserted at the end of procedure and the patient was extubated and observed over night in surgical ICU. Follow up spiral CT chest showed bronchioectatic changes in the right middle lobe, the possible cause of bronchospasm.

The common techniques to aspirate the residual volume of gastric contents are Fiberoptic gastroscopy, Indicator dilution technique and Blind aspiration via gastric tube.
In this 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 sacs29. A similar error would occur in all patients of both groups and inter-group comparisons are, therefore, valid. This method is simple, inexpensive, and easy to perform and has been widely used in the similar studies. As the effect of a drug on intragastric volume reduction is difficult to demonstrate using blind aspiration via gastric tube via gastric tube, the pH values seem preferable, therefore, for comparisons of results in the literature.

The limitation of the current study includes the use of ASAI-II patients. We should have included ASA III-V patients as well. Thus, the clinical relevance of the study may be weak. However, from efficiency point of view, we believe that the preliminary study seeking the optimal dose and timing of Omeprazole is necessary before final research assessing the usefulness of the drug in high-risk patients.
CONCLUSION: Duodenogastric reflux significantly affected both the pH and volume of gastric contents. Oral Omeprazole 40 mg administered a night before elective surgery, after excluding contaminated cases with duodenogastric reflux, provided adequate prophylaxis for the acid aspiration syndrome at the time of induction of anaesthesia.

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