# Effect of single oral dose of Famotidine administered a night before surgery on the intragastric pH and volume in adult patients undergoing elective surgery; a triple blind placebo controlled clinical trial

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**Citation**

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**Abstract**

BACK GROUND: Aspiration of gastric contents is rare, but life threatening complication of general anaesthesia. Its severity depends upon the pH and volume of gastric contents aspirated. AIMS: To evaluate the effect of preanaesthetic oral administration of Famotidine on pH and volume of gastric contents. MATERIALS AND METHODS: This triple blind, placebo controlled and randomized clinical trial was conducted on 120 adult inpatients of either sex, American Society of Anaesthesiologists physical status I-II, and aged 15-70 years. The patients in Group C (Control) received Placebo while Group F (Famotidine 40 mg) orally at 21:00 hours, a night before elective surgery. 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 analyzed for the presence of bile salts, pH and volume.RESULTS: Thirty two samples (27.35 %) out of 117 were contaminated with duodenal contents. Duodenogastric refluxate significantly affected both pH and volume of gastric contents in both Groups C &F. Famotidine did not significantly increase pH (p 0.0947), decrease volume of gastric contents (p 0.8330) and the proportion of patients (26.66 % versus 21.66%) considered" at risk" compared with Placebo (p 1.0000) according to the criteria defined (pH ≤ 2.5 and volume ≥ 25 ml). CONCLUSION: Famotidine 40 mg given orally at 21:00 hours did not provide adequate prophylaxis for acid aspiration syndrome at the time of induction of anaesthesia.Key-words: Aspiration, duodenogastric refluxate, gastric pH& volume, Famotidine.

## 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 [1]. General anaesthesia itself is a major potential risk factor that predisposes the patient to aspirate due to the loss of protective airway reflexes. Famotidine, a $H_2$ receptor antagonist, is used in peptic ulcers and other acid dyspeptic disorders of upper gastrointestinal tract in a dose of 40 mg orally once daily [2]. Our aim of study was to determine whether a single oral dose of Famotidine 40 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 refluxate. While evaluating the usefulness of Famotidine as prophylaxis for acid aspiration syndrome, the impact of duodenogastric refluxate on gastric pH and volume has not been reported in any previous study.

## MATERIALS AND METHODS

The study was approved by the College of Medicine Research Committee (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 Famotidine 40 mg, administered at 21: hours, a night before elective surgery, on intragastric pH and volume in adult 120 inpatients of either sex, aged 15-70 years of American Society of Anaesthesiologists (ASA) physical status I-II, to be intubated with cuffed endotracheal tube.

Patients with upper gastrointestinal disorders i.e. peptic ulcer, gastroesophageal reflux disease etc., Body Mass Index

(BMI) more than 40 kg/$m^2$, receiving medications known to affect the secretory and /or motor functions of the stomach, Mallampati class VI and / or mouth opening less than four centimetres and / or thyromental distance less than 6.5 centimetres and / or history of difficult intubation, intestinal obstruction, parturients, Diabetes Mellitus were excluded from the study. Patients who were premedicated and their gastric aspirates contained duodenal fluid due to duodenogastric reflux (DGR) were not included in the final statistical analysis while analyzing 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 Famotidine tablets in 120 envelopes of the same size, shape and color and their names were changed as either Drug X or Drug Y 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 X or Drug Y after the statistical analysis. On the pre-operative anaesthesia 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 F (Famotidine) randomly by this 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 21:00 hours. The patients also received oral diazepam 10 mg at the same time. According to the Hospital policy, all patients were fasted from 12 midnight irrespective of the nature of last food intake. 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. It was also recorded.

## 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 % $O_2$ 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 0.6-0.9 mg/kg rocuronium. 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 $EtCO_2$ monitor and then secured properly.

After establishing stable anaesthesia, an endotracheal tube sized 8.5 mm internal diameter coated with paraffin liquid internally as well as externally was passed via oral route into the oesophagus 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 the 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[5]. 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-millilitre 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- 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 qualitative Hay's Sulphur test for the presence of bile salts. A minimum volume of one millilitre 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 C or below) liquid. If bile salts are present Sulphur sinks down, sooner or later, in accordance with their percentage contained in the fluid.

If bile salts are present in 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 all precipitated in two or three minutes;

even in a dilution of 1:120,000 (0.0008 % or 8.33 µg/ml) precipitation occurs[6].On the other hand, if Sulphur remains floating on the surface, bile salts are absent.

Anaesthesia was maintained with Air, $O_2$ 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 (excluding contaminated samples with duodenogastric refluxate) and similarly, Group F into Group F-1(including contaminated samples with duodenogastric refluxate) and Group F-2 (excluding contaminated samples with duodenogastric refluxate) to see the impact of duodenogastric refluxate on pH and volume of gastric contents.

## STATISTICAL ANALYSIS

Statistical tests were performed using GraphPad Software, Inc., San Diego, United States, and results 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 (= ) with a power of 0.85 [7].

## RESULTS

One hundred and twenty (120) adult inpatients undergoing elective General (n=56), Orthopaedic (n=32), Gynaecological (n=20), Urology (n=four), and Thoracic (n=three), Plastic (n= three) and Neuro (n = two) Surgery were studied. Physical characteristics of patients and timings of events are shown in Table 1.

### Figure 1

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 | Group F | p-value |
|---|---|---|---|
| | n = 60 | n = 60 | |
| Age (years) | 34.77± 13.52 | 33.27±12.14 | 0.5238 |
| Sex | | | 1.0000 |
| Male | 30 (50%) | 30 (50%) | |
| Female | 30 (50%) | 30 (50%) | |
| ASA physical status | | | 0.6702 |
| Class – I | 47 (78.33%) | 44 (73.33 %) | - |
| Class – II | 13 (21.66 %) | 16 (26.66 %) | - |
| Weight (kilograms) | 74.62± 14.78 | 74.95± 14.41 | 0.9012 |
| Height (centimetres) | 161.40± 8.03 | 162.38±7.75 | 0.4980 |
| Body Mass Index (kilograms/ metre$^2$) | 28.73± 5.54 | 28.51± 5.49 | 0.8273 |
| Timings of events | | | |
| Time since premedication (minutes) | 830.75 ±134.94 | 817.42±123.18 | 0.5730 |
| Time since NPO (minutes) | 660.35±136.58 | 675.85±147.80 | 0.5519 |

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

We obtained gastric contents of 118 patients. Two patients have no gastric contents while one sample was contaminated with blood. Hay's test was performed on 117 samples and was positive in 32 patients (27.35 %). The detail is shown in Table 2.

**Figure 2**

Table 2: Facts and Figures about gastric aspirate.

| | Group C | Group F | Total |
|---|---|---|---|
| No. of cases | 60 | 60 | 120 |
| Male | 30 | 30 | 60 |
| Female | 30 | 30 | 60 |
| Sample with no gastric contents | 0 | 2 | 2 |
| Samples mixed with blood | 1 | 0 | 1 |
| Samples available for Hay's Sulphur test | 59 | 58 | 117 |
| Samples mixed with duodenal contents | 15 | 17 | 32 |
| Male | 10 | 10 | 20 |
| Female | 5 | 7 | 12 |

Duodenogastric refluxate significantly affected both the pH and volume of gastric contents in both Groups C & F as shown in Table 3.

**Figure 3**

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

| Variables | Group C | | Group F | |
|---|---|---|---|---|
| | n= 60 | | n= 60 | |
| | Group C-1 | Group C-2 | Group F-1 | Group F-2 |
| | n = 59 | n = 44 | n = 58 | n = 41 |
| pH | 2.74±1.93 | 1.73±0.46 | 2.91 ±1.86 | 1.90±0.45 |
| Volume (millilitres) | 30.31±25.10 | 21.28±18.44 | 31.12±24.90 | 20.42±18.90 |

Note: Group C-1 and GroupF-1 represent Groups including contaminated samples with duodenogastric refluxate.
Group C-2 and Group F-2 represent Groups excluding contaminated samples with duodenogastric refluxate.
Comparison of pH between Group C-1 and Group C-2 (p value 0.0010).
Comparison of pH between Group F-1 and Group F-2 (p value 0.0007).
Comparison of volume between Group C-1 and Group C-2 (p value 0.0016).
Comparison of volume between Group F-1 and Group F-2 (p value 0.0467).
Comparison of pH between Group C-2 and Group F-2 (p value 0.0947).
Comparison of volume between Group C-2 and Group F-2 (p value 0.8330).

There was no statistically significant difference between the two Groups C-2 and F-2 (non- contaminated samples with duodenogastric refluxate) regarding pH (p 0.0947) and volume (p 0.8330) of gastric contents.

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.

**Figure 4**

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

| Variables | Group C-2 | Group F-2 | p- value |
|---|---|---|---|
| | n = 44 | n = 41 | |
| Patients with pH ≤ 2.5 | 39 (88.63 %) | 39 (95.12 %) | 0.4351 |
| Patients with volume ≥25 ml | 11(25.00 %) | 11(36.66%) | 1.0000 |
| Patients with pH ≤ 2.5 and volume ≥25 ml | 11(25.00%) | 11(36.66%) | 1.0000 |

Note. Samples mixed either with duodenal contents (32) or blood (one) or having no contents (two) are not included.

There was also no statistically significant difference between the two Groups C-2 and F-2 (p 1.0000).

No side effect of study drugs was noted. All patients were discharged from the hospital without any problem.

## DISCUSSION

Many pharmacological attempts, including the use of $H_{2}$-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]. We searched on PubMed (www. Pubmed.gov) under "aspiration of gastric contents and Famotidine" and found 14 articles. These studies did not match exactly with our study. However, we compared our results with those studies which were very close to our study in term of dose, timing of dose, nature of surgery and age group. Vila et al [9] 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. Famotidine produced a significant decrease in gastric volume and acidity. No Patient was considered to be at risk according to criteria defined pH < 2.5 and volume > 0.4 ml.kg-1. Gallagher et al [10] compared famotidine 40 mg, ranitidine 300 mg and placebo given in a single oral dose at 2200 hours as the sole means of prophylaxis in 286 patients who underwent elective surgery the following day. They concluded that the administration of a potent $H_{2}$-antagonist

Famotidine in a single oral dose at night offers a convenient routine means of providing extensive prophylactic cover in patients scheduled to undergo elective surgery the following day. Similarly, Camerini et al [11] compared the effects of two $H_2$-antagonist drugs (Famotidine and cimetidine) on both volume and acidity of gastric secretions. In the Famotidine group no patient showed pH less than 2.5 and gastric secretions volume greater than 25 ml. Heim et al[12] on the other hand, found that during induction and in the following 30 min, in the famotidine treatment group 28.7% of all pH values were pH less than 2.5, as against 45.4% in the control group (P = 0.08).They concluded that Famotidine 40 mg given orally at 10.00 p.m. on the evening before surgery is not a reliable means of decreasing intragastric acidity or, consequently, of preventing of acid aspiration syndrome. Although there are lot of studies conducted on Famotidine for the prophylaxis of acid aspiration syndrome but technically our results are more accurate because we considered only those samples that were negative for bile salts. Is there any significance of duodenogastric reflux? The answer is, of course: yes. Duodenogastric refluxate raises the pH to towards less acidity and at the same time increases the volume of gastric contents. In this way, we are studying effect of Famotidine or other drugs similar in action on gastric secretions and results are of not true gastric secretions rather gastric secretions mixed with duodenal fluid. Famotidine is old drug and is still in use and not withdrawn from the market.

Aspiration of gastric contents (Mendelson's syndrome) was first described by Mendelson CL in 1946 in obstetrical cases. 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 anaesthesia literature. In all the previous studies conducted, importance of duodenogastric reflux, 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 [1314] with variable incidence. Keet et al [15] reported 33%, Raved et al [16] 8.98 % and Wolverson et al [17] 46% incidence of duodenogastric reflux in healthy subject.

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 [18]. When duodenal contents flow in retrograde fashion, then mix with acid and Pepsin[14] 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.

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 [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 oesophagus may be occluded by inflated endotracheal tube cuff and can interfere with stomach tube insertion. Secondly, this technique also avoids finding the upper oesophageal 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. 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 oesophagus 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 Bilitec™ 2000 ambulatory bile reflux recorder is currently the only commercially available device that is proven effective in measuring bile reflux. Using Bilirubin as a marker for bile, the Bilitec 2000 recorder captures the frequency and duration of bile exposure either in the stomach or oesophagus 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 [19] depends on the principal that bile salts have the property of reducing the surface tension of fluids in which they are contained [20], was devised in1886 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 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 sacs. 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.

In this study one sample was 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 pH of blood mixed with gastric contents rather than pure gastric contents. However, any sample containing any amount of visible blood mixed with gastric contents was not considered for pH and volume analysis.

## CONCLUSION

Oral Famotidine 40 mg administered a night before elective surgery, did not provide adequate prophylaxis for the acid aspiration syndrome at the time of induction of anaesthesia. For better results two consecutive doses of Famotidine 40 mg with the addition of a prokinetic agent seems to be more appropriate but further work is required in this regard.

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