

EFFECT OF CIMETIDINE ON REDUCTION OF GASTRIC SECRETION AND pH IN ADULT PATIENTS UNDERGOING ELECTIVE SURGERY AND ITS IMPACT ON ASPIRATION RISK

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Background: Aspiration of gastric contents is rare, but serious and life threatening complication of general anaesthesia. Its severity depends upon the pH and volume of gastric contents. **Methods:** This study was conducted to evaluate the effect of pre-anaesthetic administration of oral Cimetidine on pH and volume of gastric contents in 116 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 T (Cimetidine 800 mg) orally at 9 PM, 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 analysed for the presence of bile salts, pH and volume. **Results:** Thirty-two samples (28.31%) out of 113 were contaminated with duodenal contents. Duodenogastric refluxate significantly affected both the pH and volume of gastric contents in both groups. Cimetidine, after excluding contaminated cases either with duodenogastric refluxate or blood, did not significantly increase the pH ($p=0.1221$), decrease the volume of gastric contents ($p=0.0816$) and the proportion of the patients (25.64% versus 23.80%) considered “at risk” compared with Placebo ($p=1.0000$) according to the criteria defined ($pH \leq 2.5$ and volume ≥ 25 ml). **Conclusion:** Cimetidine 800 mg given orally at 9 PM did not provide adequate prophylaxis for acid aspiration syndrome at the time of induction of anaesthesia.

Keywords: Aspiration, duodenogastric refluxate, gastric pH and volume, Cimetidine.

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 anaesthesia 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 Anaesthesiology.

Cimetidine, an H₂-receptor antagonist, is used in peptic ulcers and other acid dyspeptic disorders of upper gastrointestinal tract in a dose of 800 mg orally once daily.² Our aim of study was to determine whether a single oral dose of Cimetidine 800 mg, administered a night before surgery, is effective in increasing the pH to 2.5 or more and decreasing volume to 0.4 ml/kg or less, or 25 ml in adult patients undergoing elective surgery by excluding those cases contaminated with duodenogastric refluxate. While evaluating the usefulness of Cimetidine as prophylaxis for acid aspiration syndrome, the impact of duodenogastric refluxate on gastric pH and volume has not been reported in any previous study.

MATERIAL AND METHODS

This study was done at Department of Anaesthesia and Department of Physiology, King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia. The College of Medicine Research Centre (CMRC) and College Ethics Committee approved the study. Written informed consent was obtained from all the patients.

Patients and group assignment

We examined the effect of single oral dose of Cimetidine 800 mg administered at 9 PM, the night before elective surgery, on intragastric pH and volume in 116 adult 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, 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 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 & 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 final statistical

analysis while analysing 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 Cimetidine tablets in 116 envelopes of the same size, shape and colour and their names were changed as either 'Drug One' or 'Drug Eleven' 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 Eleven' 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 (randomisation). Thus, the patients were allocated either to Group C (Control) or Group T (Cimetidine) 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 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 after 12 mid - night. 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% O₂ by face mask using four breaths vital capacity method, 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. Placement and position of endotracheal tube was confirmed with EtCO₂ 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 in 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 tube³ (Jamjoom Medical Industries, Jeddah, Saudi Arabia) sized 18F 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.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 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 one ml were considered as no gastric contents because a minimum volume of one ml of gastric contents was sufficient for pH-metry. 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 ml 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.

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 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, O₂ and sevoflurane. 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 pre-medication, 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 duodeno-gastric refluxate) and Group C-2 (excluding contaminated samples with duodenogastric refluxate) and similarly Group T into Group T-1 (including contaminated samples with

duodenogastric refluxate) and Group T-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 were 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 pre-medication, 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 sixteen (116) adult inpatients undergoing elective General (n=54), Orthopaedic (n=32), Gynaecological (n=18), Urology (n=5), and Thoracic (n=3), Plastic (n=2) and Neuro-Surgery (n=2) 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 pre-medication and time since NPO.

We obtained gastric contents of 113 patients. Two patients had no gastric contents while one sample was contaminated with blood. Hay’s test was performed on 113 samples and was

positive in 32 patients (28.31%). The detail is shown in Table-2.

The average (range) pH and volume of contaminated cases with duodenal contents were 5.51 (1.63–6.98) and 56.87 (9.0–112.0) ml and blood 7.13 and 4.0 ml. These cases were considered as contaminated and not included in statistical analysis while analysing 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 no statistically significant difference between the two Groups C-2 and T-2 (non-contaminated samples with duodenogastric refluxate) regarding pH (p=0.1221) and volume (p=0.0816) of gastric contents. Group C-1 and Group T-1 represent Groups including contaminated samples with duodenogastric refluxate. Group C-2 and Group T-2 represent Groups excluding contaminated samples with duodenogastric refluxate. Comparing pH between Group C-1 and Group C-2, p-value was 0.0010 and comparing pH between Group T-1 and Group T-2, p-value was 0.0008. Comparison of volume between Group C-1 and Group C-2 gives p-value=0.0373 and comparison of volume between Group T-1 and Group T-2 gives p-value=0.0239. Comparing pH between Group C-2 and Group T-2, p-value=0.1221 while comparing volume between Group C-2 and Group T-2, p-value= 0.0816.

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 duodenogastric refluxate. There was also no statistically significant difference between the two Groups (p=1.0000).

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

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=58)	Group T (n=58)	p-value
Age (years)	34.29±13.14	33.21±12.07	0.6438
Gender			1.000
Male	29 (50%)	29 (50%)	
Female	29 (50%)	29 (50%)	
ASA Physical Status			1.000
Class-I	45 (77.58%)	42 (72.41 %)	
Class-II	13 (22.41 %)	16 (27.58 %)	
Weight (kilograms)	73.91±14.42	75.35±14.45	0.5923
Height (centimetres)	161.34±7.99	162.49±7.28	0.4212
Body Mass Index (kilograms/ meter ²)	28.62±5.53	28.50±5.49	0.9056
Timings of events			
Time since premedication (minutes)	831.16±136.92	820.24±121.06	0.6501
Time since NPO (minutes)	673.79±149.84	661.09±138.56	0.6363

Table-2: Facts and figures about gastric aspirate.

	Group C (n=58)	Group T (n=58)	Total (n=116)
Sample with no gastric contents	0	2	2
Samples mixed with blood	1	0	1
Samples available for Hay's Sulphur test	57	56	113
Samples mixed with duodenal contents	15	17	32
Male	9	10	19
Female	6	7	13

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

Variables	Group C (n=58)		Group T (n=58)	
	Group C-1 (n=57)	Group C-2 (n=42)	Group T-1 (n=56)	Group T-2 (n=39)
pH	2.78 \pm 1.74	1.74 \pm 0.46	2.95 \pm 1.83	1.90 \pm 0.46
Volume (ml)	30.11 \pm 25.02	20.58 \pm 18.44	32.08 \pm 24.81	21.24 \pm 19.02

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

Variables	Group C-2 (n=42)	Group T-2 (n=39)	p- value
Patients with pH \leq 2.5	39 (92.85 %)	38(97.43 %)	0.6165
Patients with volume \geq 25 ml	10 (23.80 %)	10(25.64%)	1.0000
Patients with Ph \leq 2.5 and volume \geq 25 ml	10 (23.80%)	10(25.64%)	1.0000

Samples mixed either with duodenal contents (32) or blood (1) or having no contents (2) are not included.

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 Anaesthesia.⁸ 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 (www.Pubmed.gov) under 'aspiration of gastric contents and Cimetidine' and found 14 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 in term of dose, route of administration, timing of dose, nature of surgery and age group. We found only one study that was very close to our study but effervescent cimetidine 800 mg was given 2 hours before surgery. In this study Bouly *et al*¹⁰ found gastric pH were significantly higher in the three treated groups than in control ($p < 0.01$). Omeprazole and cimetidine were equally effective in reducing volume and pH of the gastric juice at the beginning and at the end of anaesthesia. Our results do not agree with this report due to timing of administration of

Cimetidine and duodenogastric reflux. Our results are more accurate because we excluded samples contaminated with duodenogastric refluxate.

Aspiration of gastric contents (Mendelson's syndrome) was first described by Mendelson CL in 1946 in obstetrical cases.¹¹ 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 (DGR), as a possible factor that can affect both the pH and volume of gastric contents, has never been addressed. Duodenogastric reflux, the transpyloric retrograde flow of duodenal contents into the stomach, is well known, well established clinical entity¹²⁻¹⁶ 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 Keet¹⁷ and Huges *et al*,¹⁸ 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 al*,¹⁹ studied 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. Cholecystokin in 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 understood²⁰. Our reported incidence 29.66% is less than the 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.²¹ 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 analysing pH and volume of gastric contents. Lastly, the average (range) volume of contaminated cases with duodenal contents was 56.87 (9.0–112.0) 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 oesophagus. Although, this technique of passing stomach tube is old⁴, 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. In the awaked state, the basal rate of saliva production is about 0.5 ml/minute, but this may increase to 5

ml/minute 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 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.²³ 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 test²⁴ depends on the principle that bile salts have the property of reducing the surface tension of fluids in which they are contained,²⁵ 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 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.²⁶ 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. 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.²⁷ However, any sample containing any amount of

visible blood mixed with gastric contents was not considered for pH and volume analysis.

The limitation of the current study includes the use of ASA I-II patients. We should have included ASA III-IV 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 Cimetidine is necessary before final research assessing the usefulness of the drug in high-risk patients.

CONCLUSION

Oral Cimetidine 800 mg administered a night before elective surgery, did not provide adequate prophylaxis for the acid aspiration syndrome at the time of induction of anaesthesia.

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